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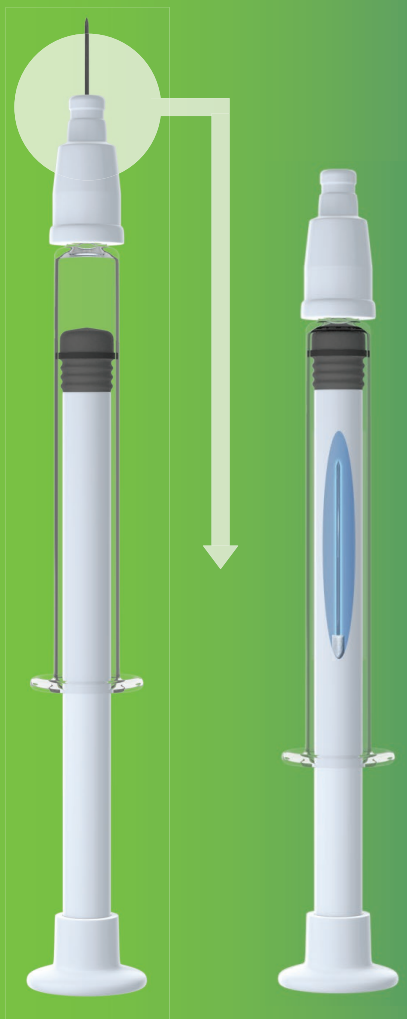

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ONdrugDelivery Issue N° 61, October 6th, 2015

Prefilled Syringes

This edition is one in the ONdrugDelivery series of publications from Frederick Furness Publishing. Each issue focuses on a specific topic within the field of drug delivery, and is supported by industry leaders in that field.

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AUTO INJECTORS & PEN INJECTORS: A USER-CENTRIC DESIGN APPROACH

In this article, SHL Group provides insights into their injection device design processes and culture, emphasising their focus on the patient throughout the design journey. Their latest device, Penny™, is introduced – an adjustable multi-dose disposable injector. SHL also examines trends in injector design and makes two broad predictions: a greater adoption of simpler, unadorned, disposable devices, and the rise of technology integration and in particular connected devices.

With the momentum of self-administered injection trends quickly increasing, devices for self-injection, like auto injectors and pen injectors, are no longer a foreign concept to many patients. Device designs are thus now focused more than ever on a user-centric approach – with the application of human factors / usability engineering crucial to minimise user-related risks and enhance ease-of-us. Early involvement of targeted patient groups in user studies during the research and development stages helps engineers not only to understand patient dynamics better but also ensure patients' needs are fully integrated into the design of the device. For example, patients with rheumatoid arthritis (RA) may have serious dexterity issues that hinder their ability to uncap or grip a device and properly administer the injection. An example of an auto injector designed to address such needs is SHL's Amber® Auto Injector, a device with customised uncapping or grip options and an exterior that provides additional friction for an easier grip (Figure 1).

Another example of a user-centric device that has experienced much market success is the Emerade® Auto Injector, an intuitive disposable two-step auto injector designed

Figure 1: A rheumatoid arthritis patient handles the Amber® Auto Injector and provides positive feedback to SHL design engineers. SHL's Amber™ Auto Injector is a simple ergonomic two-step auto injector that leverages SHL's market-proven Pushclick® technology.

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to deliver adrenaline for emergency use via intramuscular injection. A usability study of the accuracy of Emerade® device use in a simulated emergency demonstrated that all of the participants successfully administered the injection as per the labelled instructions.

HUMAN FACTORS, ERGONOMICS AND USABILITY ENGINEERING

The role of an industrial designer (Figure 2) is to create and execute design solutions for problems of form, usability, and the general physical ergonomics. The industrial designer's contributions should be seen as improved service for the patient to self-administer the medication. Equally important, good design is for everyone; understanding user needs is essential to offer users the most suitable drug delivery design available.

Specific patient characteristics, including age and strength, which may impact physical and cognitive capabilities, should be considered when choosing a device design. Precise communication between the device partner and the biopharmaceutical company is thus paramount, especially during early stages where design input requirements are specified. Aside from understanding the targeted user group, the designers also need to gain knowledge of the anticipated usage environment as well as anticipated limitations. These could range from dexterity issues or impaired vision as a result of chronic diseases to simple, intuitive devices that the patient feels comfortable self-administering.

Various aspects for optimising device performance – like portability, identification, safety and effectiveness – should always be considered during early design phases. For a device to be portable and identifiable, the device engineer has to think about size, shape, colour and labelling, whereas device safety and reliability may require fool-proof safety designs such as trigger-locking and automatic safety locking features to prevent injury after use. User-friendliness and effectiveness can depend on optimal grip designs tailored to specific patient types or just size in general. The overall design should be based on a mixture of proven design features and current user study results, and iterated to ensure that the most optimal design is outputted before entering manufacturing stages. Figure 3 summarises functionality and usability considerations for auto injector design.

Other essential considerations include storage of the device, expected delivery timelines and design requirements, such as whether or not the device should be based on an existing platform or created as a completely new system. Requirements include but are not limited to accommodating various primary containers as well as increased agent drug viscosities or volumes.

Figure 2: An SHL Industrial Designer sketches a conceptual design of an auto injector.

Auto injectors and pen injectors are intended to assist the end-user with the self-injection process and are often self-administered by the patients themselves. Consequently, applying Human Factors Engineering (HFE) principles is crucial as

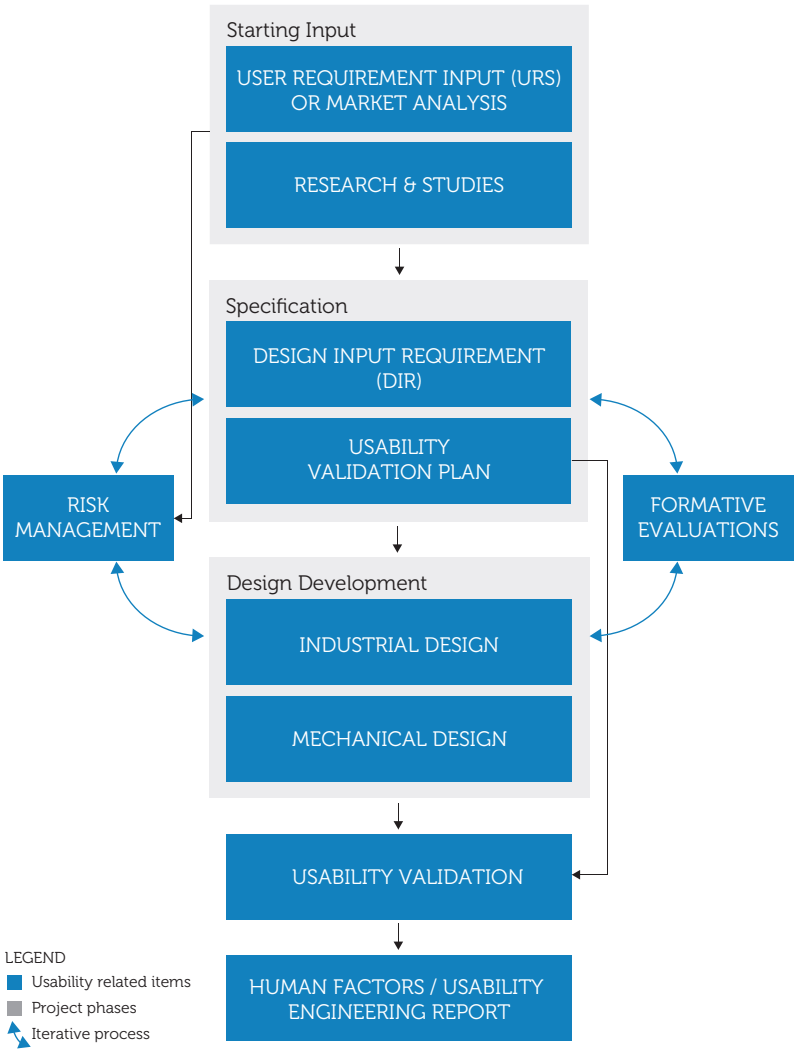

Figure 3: A simplified functionality usability flowchart for the design and development of auto injectors.

Figure 4: The needleless Molly® trainer helps users simulate the two-step operation of the actual auto injector. The trainer is paired with a reset mechanism in the cap, allowing the device to be used as many times as needed until the user is ready to inject with the real device.

incorporated physical and psychological characteristics minimise user-related risks and enhance user compliance.

HFE / Usability Engineering should be applied throughout the entire product development process and assists with key design decisions. Depending on the nature and stage of the project, various usability tools are applied to the process, including but not limited to user-performance studies, interviews, on-site visits, failure mode effects analysis (FMEA), review of existing ergonomic research, and design guidance.

DESIGNING FOR MANUFACTURABILITY

Besides HFE, one of the biggest challenges for the device designer/manufacturer is to develop a device that is easy to understand, intuitive to handle, has a non-medical appearance, and also suitable for mass production. Hence the importance of DFM (Design for Manufacturing) aspects of designing auto injectors and pen injectors, as economic factors will affect the production of the device. This normally would require close collaboration and instant communication between industrial design engineers, production teams and project managers. SHL offers in-house availability of key design services and manufacturing capabilities. The result is a faster track towards a finalised product for mass production. Other services may include industrial design, regulatory affairs, and quality control systems; and capabilities such as tooling, moulding, assembly, and final assembly. Having in-house capabilities accelerates time-to-market for new products and for new features of existing products.

Consequently, a balance must be achieved between the pharmaceutical company and the device manufacturer. It is important for both parties to understand the design concepts and usability programs clearly, and to also share valuable knowledge from past experiences.

ENHANCE AND IMPROVE USER EXPERIENCE

According to the World Health Organization, "Poor adherence attenuates optimum clinical benefits and therefore reduces the overall effectiveness of health systems." While auto injector designers strive to introduce the most innovative and user-centric device solutions, oftentimes even the most intuitive device cannot overcome a patient's anxiety when faced with their first self-administered injection.

Not only do the considerations of safety, convenience, and ease of use need to be integrated into the device design to begin with, the pharmaceutical company and device manufacturer will need to work together to anticipate potential usage scenarios and prepare supporting documents such as clear instructions for use (IFUs), handling videos, appropriate labelling and training devices. Since injection devices like auto injectors are usually targeted for self-administration, where the patient received the device with drug inside through a distribution channel and takes the injections by themselves without the direct supervision of a healthcare professional, it becomes even more challenging for the biopharmaceutical company to effectively connect with the patient to ensure the proper usage of the device.

SHL provides needle-free trainers, for example the trainer version of Molly® shown in Figure 4, that replicate both the look and feel of the actual device, in order to lessen the impact of patient's psychological barrier. Trainers can prove to be very effective and provide users with an opportunity to practice handling the device without the fear of incorrect administration.

Understanding user needs goes beyond identifying factors such as the force required to operate a device or the most comfortable grip – at times it is the user's emotional status that will make or break the deal. Indeed, while an auto injector or a pen injector may be simple to use, it is an obsolete device if the user is afraid to use it. Therefore device manufacturers like SHL steer away from the typical medical device look to enhance acceptance level from patients.

Improving patient compliance will ultimately enhance wellness and a better health management. SHL strives to improve adherence, and in doing so must assess the various aspects that surround the everyday concerns of a patient who will be using self-administered injection devices like auto injectors and pen injectors on a regular basis.

INNOVATING TO EVOLVE – "PENNY™ ADJUSTABLE MULTI-DOSE INJECTOR"

True user-centric innovation should be based off of proven designs, user study results, or even just market observations – which may include user complaints. By understanding the missing features or possible room for improvement of similar existing devices and leveraging recognised preferences, the designer can truly design to further evolve a device. An example is SHL's latest device - Penny™, a 3.0 mL multi-dose disposable pen injector with a user-centric and simple yet modern industrial design (see Figure 5).

Figure 5: Penny™ Adjustable Multi-Dose Injector - a 3.0 mL multi-dose disposable pen injector with a user-centric and simple yet modern industrial design.

While similar pen injector products have been available on the market for many years, Penny™ is designed to stay true to the established mentality of a diabetic user and offers equivalent performance to current leading pen injector products. Internal user studies also showed that the discreet design was preferred and the interface intuitive and easy to use at home (Figure 6).

The business model offered by Penny™ also allows for full freedom to operate (FTO) and a short time to market if a pre-configured device is chosen. The device offers a platform for variable as well as set doses and is designed for large scale manufacturing.

UPCOMING TRENDS IN THE INDUSTRIAL DESIGN OF AUTO INJECTORS

In an industry where long development cycles and time-consuming product approval processes make trends difficult to recognise, a user-centric approach will always be the basis for the industrial design of auto injectors and pen injectors. In the future, a greater number of unadorned, disposable devices with even more simplified performances will become preferred and stay mainstream. In addition, these devices could potentially have the ability to connect to smart communication systems, for improved compliance and potentially reducing costs.

Figure 6: A patient injecting with the Penny™ device in the comfort of their own home.

A focus from incident-based treatment and care delivery has been shifted towards continuous disease management, thus patient engagement has become more crucial than ever. Integrating technologies such as connectivity can enhance information sharing, allowing for better management of patient treatments and device tracking. With internet and electronics readily available today and technology penetration apparent and still growing, such solution can be easily adopted. It is thus safe to assume that more technology-integration innovations will be introduced alongside the continuous innovation of the industrial and mechanical design of auto injectors and pen injectors.

SHL offers a range of auto injector and pen injector solutions (Figure 7) that can accommodate changing injection needs such as higher viscosity, larger volumes, and more.

Figure 7: SHL's range of auto injector and pen injector solutions that can accommodate changing injection needs such as higher viscosity, larger volumes, and more.

TriboFilm Research, Inc.

NEXT-GENERATION LUBRICATION SOLUTIONS FOR PHARMACEUTICAL PACKAGING

In this article, appearing for the first time in ONdrugDelivery Magazine, we're pleased to introduce Jackson D Thornton, PhD, Senior Research Scientist; Daniel E Jonsen, PhD, Principal Scientist; and Vinay Sakhrani, Vice-President, Technology, all of TriboFilm Research Inc. Here, they discuss the importance of lubrication in prefilled syringes, especially in auto injector applications, outline some of the drawbacks of traditional silicone oil-based lubrication, and describe a novel Atmospheric Plasma Technology, which immobilises lubricants (including silicone and TriboFilm's own PFPE-based next generation lubrication system) onto glass and polymer primary container surfaces.

A prefilled syringe offers several advantages in pharmaceutical packaging and delivery over the conventional combination of a vial and a disposable syringe. These advantages, which have driven the growth of the prefilled syringe industry at an astonishing rate in recent years, include:

- Accurate drug dosing
- No overfill requirement – the US FDA requires up to 25% overfill for vials
- No preservatives required in the formulation
- Increased assurance of sterility
- Ease of use
- Patient comfort and compliance
- Time savings in emergency situations
- Reduced materials cost
- Less waste and lower environmental impact

A prefilled syringe is traditionally defined as a three-part device with the following components:

(1) the syringe barrel, made of either glass or plastic, which can be formatted with a staked needle or a luer fitting;
(2) a rubber plunger that provides container closure integrity; and
(3) a plastic plunger rod used to advance the plunger.

However, all syringes also contain an invisible fourth component, the lubricant, which is often overlooked and can have a major impact on the syringe function and drug stability. Figure 1 depicts the four components in a typical prefilled syringe.

"Ideally, the industry would like a universal immobilised-lubricant syringe system applicable to glass and plastic syringes of all formats, which has consistent plunger forces and adds no particles to the drug medium"

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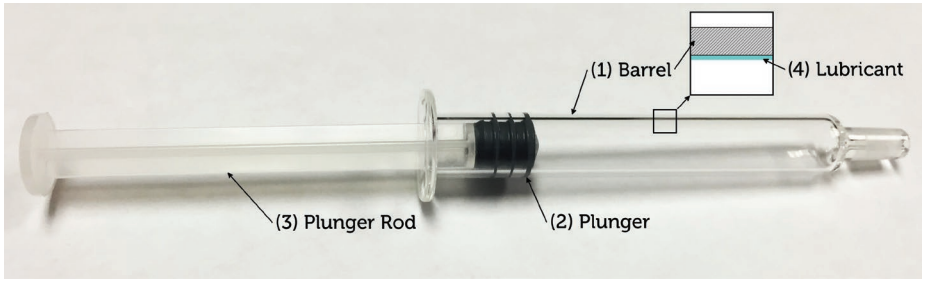


Figure 1: Anatomy of a four-part syringe.

SILICONE OIL: THE INVISIBLE RISK IN PREFILLED SYRINGES

A prefilled syringe requires a lubricant to enable the plunger to move properly through the barrel. The traditional industry standard lubricant for prefilled syringes is silicone oil. However, silicone oil tends to migrate and is easily displaced from its original application area. Silicone oil migration can affect the mechanical function of a syringe in two significant ways. First, as the oil migrates off of the syringe barrel and into the product, some areas of the barrel may become lubricant-depleted. This will significantly increase the glide force required to move the plunger over these regions. Second, the plunger must exert compressive forces against the barrel surface in order to seal properly. Since the plunger remains stationary during storage, the long-term compressive forces exerted at its storage position cause the silicone oil in this region to be displaced, i.e. "squeezed out" over time. This increases the break-loose force required to overcome the static friction of the plunger and start moving it from its storage position.

Both increased glide forces and increased break-loose forces can cause significant problems when a prefilled syringe is used in the increasingly popular auto injector format. The increased glide force required at lubricant-depleted points along the barrel can significantly slow the motion of the plunger, often to the point that the overall injection time becomes unacceptably long. In more severe cases, where the force of the advancing spring is lower than the required travel force, the plunger will stop entirely, resulting in incomplete injection. Furthermore, if the force of the spring on the plunger exceeds the strength of the syringe flange, the flange will break, resulting in device failure and a potentially serious safety issue. All of these issues associated with lubrication problems have resulted in numerous recalls for auto injector devices.

The migration of silicone oil into the drug product can also generate unwanted sub-visible particles. Agitation during shipping, formulation excipients, and plunger movement during injection can all exacerbate this problem. Recently, a number of publications have shown that suspended silicone oil particles may cause protein-based pharmaceutical molecules to aggregate.[1-3] These particles introduce several product quality concerns, such as exceedance of USP limits for particulates in parenteral containers,[4] structural instabilities in proteins caused by adsorption,[5] and/or immunogenic responses caused by injection of silicone oil induced protein aggregates or silicone oil/protein complexes.[5-6] The latter two of these problems can result in significantly reduced drug efficacy and/or potentially dangerous reactions in the patient, making the product unfit for use. In fact, several biopharmaceutical drugs carry a strict warning to avoid using a siliconised syringe to deliver the drug, as doing so would render the drug ineffective and dangerous[7-9].

PRODUCT QUALITY PROBLEMS ASSOCIATED WITH SILICONE OIL MIGRATION

- Higher, more erratic plunger forces
- Sub-visible silicone oil particles in the product
- Protein aggregation and immunogenic responses

The pharmaceutical industry has actively sought solutions to the shortcomings of silicone oil, and a few alternatives are available. Several manufacturers promote a "baked-on" silicone lubricant for glass prefilled containers where the siliconised glass barrel is heated to a high temperature. Reduction of the extractable silicone oil is attributed to the vaporisation of the lower-molecular-weight silicone molecules during the baking process. However, because the temperatures used are too high for both plastic syringes and staked-needle glass syringes, the silicone baking process is only applicable to glass luer cone syringes and cartridges. Another alternative is to reduce the amount of silicone in the syringe system, with the resulting compromise of higher plunger forces. Additionally, some companies are exploring the use of laminated plungers that do not require a lubricant on the syringe barrel. However, these plungers will not work with the industry standard glass containers as they are compatible only with plastic syringes. Ideally, the industry would like a universal immobilised-lubricant syringe system applicable to glass and plastic syringes of all formats, which has consistent plunger forces and adds no particles to the drug medium. An immobilised lubricant would give the pharmaceutical industry another option for their delivery systems and would allow silicone-sensitive formulations to be provided in a prefilled format.

TRIBOFILM'S ADVANCED LUBRICATION SOLUTIONS

TriboFilm Research has developed Atmospheric Plasma Technology that can immobilise a lubricant onto a pharmaceutical container surface. TriboFilm's advanced lubrication technologies include TriboLink-Si™, a superior silicone oil based lubrication technology; and TriboGlide-DS™, a high-performance next-generation lubricant system based on perfluoropolyether (PFPE) chemistry. Both TriboLink-Si™ and TriboGlide-DS™ use a Downstream Atmospheric Pressure Plasma process to crosslink the lubricant onto the container as seen in Figure 2.

What is atmospheric pressure plasma? Physicists define plasma as the fourth state of matter, which can be described in simple terms as an ionised gas. It is composed of ions, electrons, photons, and excited neutral atoms or molecules. Examples of plasma from common experience include flames, lightning, and the glowing medium inside a neon lamp. While most plasmas used in industrial processes must be generated under vacuum, which greatly increases costs and severely limits their applications, TriboFilm has developed

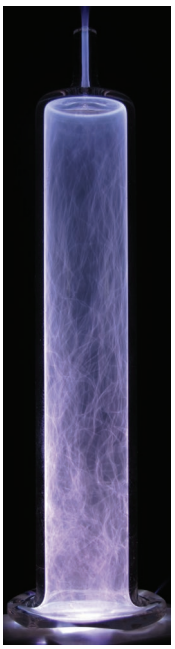


Figure 2: Syringe filled with downstream atmospheric pressure plasma during crosslinking treatment.

a unique low-cost atmospheric pressure plasma process that requires no vacuum and can operate in open air. Therefore this low-cost system can easily be integrated inline into a continuous process for syringe manufacturing. TriboFilm's atmospheric plasma process uses only inert gas, which eliminates any risk of exposing the syringe contents to unwanted reaction by-products that are typical of other crosslinking techniques. Further, this process uses a patented downstream plasma configuration, where the plasma is generated in one location, then flows "downstream" to a second location where the part is processed. This is beneficial in that the resulting treatment is gentler on the lubricant and syringe, and since no electrodes or other foreign objects enter into or come in contact with the syringe, contamination with foreign material becomes much less likely.

The crosslinking of the lubricant onto the syringe barrel greatly reduces its mobility, which has two important benefits. First, the rate of displacement of the lubricant by the syringe plunger during storage is significantly reduced, thereby reducing the break-loose force. Second, the tendency of the lubricant to migrate off of the syringe barrel and into the drug product is also reduced, resulting in fewer sub-visible particles and less potential for aggregation of protein-based pharmaceuticals.

Both TriboLink-Si™ and TriboGlide-DS™ are applied by the following steps (Figure 3):

1. The syringe surface is pre-treated with downstream atmospheric plasma to prepare the surface and enhance its wettability by the lubricant precursor.
2. The appropriate high-purity lubricant precursor is sprayed onto the syringe surface using a diving nozzle to ensure uniform application.
3. The sprayed-on lubricant precursor on the syringe surface is exposed to a second downstream atmospheric plasma treatment, which crosslinks it into an immobilised gel with superior lubricating properties.

BENEFITS OF TRIBOFILM'S LUBRICATION PROCESSES

- Downstream Atmospheric Plasma crosslinks the lubricant onto the device surface
  - Reduced lubricant migration
  - Fewer sub-visible particles than free oil
  - Lower plunger forces with no stick-slip behaviour during movement
- Scalable process compatible with inline, continuous manufacturing
- Applicable on glass, plastic (e.g. COP, COC, PP), and metals (e.g. needles)
- Compatible with staked-needle and luer syringe formats
- Both silicone and silicone-free options available

LUBRICANT PERFORMANCE STUDIES

As established above, low break-loose forces and consistent, low glide forces can be critical factors in the reliability, dosing accuracy, and ease of use of a prefilled syringe, especially when used in an auto injector. In addition, sub-visible lubricant particles can also play a major role in the shelf life, efficacy, and safety of the product in a prefilled syringe. The superiority of the TriboLink-Si™ and TriboGlide-DS™ lubrication systems over traditional silicone oil and baked-on silicone lubricants was demonstrated on glass syringes by evaluating the corresponding syringe force profiles and particulate loads.

> "Standard plunger designs are compatible with both TriboLink-Si™ and TriboGlide-DS™, with no changes in material or design required to maintain container closure integrity. Both of these lubricants are compatible with glass and plastic pharmaceutical containers"

Syringe Force Testing

Syringe force testing was performed on 1 mL long glass syringes with 0.5 inch long 27 gauge needles. Syringes lubricated with silicone oil, TriboLink-Si™, and TriboGlide-DS™ were filled with a solution of 0.05% Polysorbate 80 in sterile filtered water. The polysorbate surfactant is commonly used with protein-based pharmaceuticals and provides a challenging test case for syringe performance measurements. Groups of samples were aged for 2, 4, and 12 weeks at 40°C. Plunger force measurements were performed using a Zwick/Roell Z0.5 force tester at 100 mm/min. Ten samples were prepared for each of the nine experimental conditions.

Figure 4 shows a series of force-displacement curves for silicone, TriboLink-Si™, and TriboGlide-DS™ lubricated syringes after 12 weeks of storage at 40°C. As shown in the figure, the break-loose force (F_B) is defined as the peak force required to overcome static friction, and the glide force (F_G) is defined as the force required to maintain gliding motion after breaking the plunger loose. Note the relatively high F_B and F_G values for silicone oil compared to both TriboLink-Si™ and TriboGlide-DS™. In addition, a high degree of inconsistency is seen among the samples with silicone oil lubrication compared to those with TriboLink-Si™ or

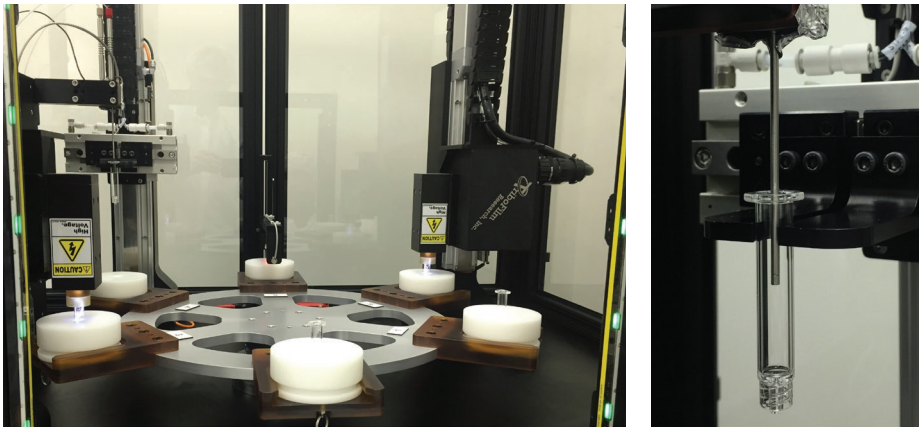
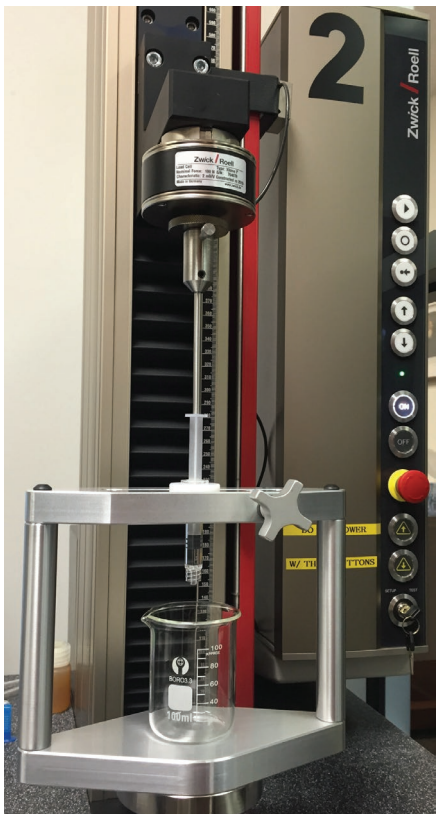


Figure 3: Left, Syringes receiving TriboGlide-DS™ treatment on TriboFilm's automated processing system. Note the live pre-spray surface activation plasma and post-spray crosslinking plasma at 8 o'clock and 2 o'clock positions, respectively. Right, Close-up of syringe receiving dynamic PFPE spray (the station at 10 o'clock position in left-hand image) during TriboGlide-DS™ application process.



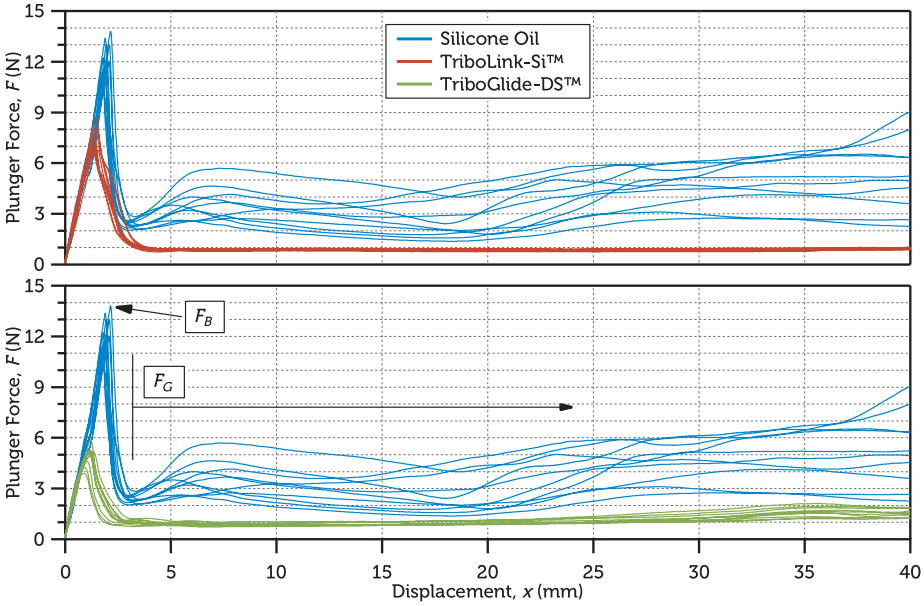


Figure 4: Force-Displacement curves for silicone oil, TriboLink-Si™ and TriboGlide-DS™ lubrication systems acquired using one of TriboFilm's Zwick Z0.5 Force Testers (left). Break-Loose Force (F_B) is defined as the maximum force required to break the static friction of the plunger. Glide Force (F_G) is defined as the force required to maintain plunger movement once static friction has been overcome. All samples are 1 mL long glass syringes filled with a 0.05% Polysorbate 80 solution in sterile filtered water. All samples were stored for 12 weeks at 40°C and agitated for 24 hours just prior to characterisation.

TriboGlide-DS™ lubrication. The higher break-loose forces measured for the silicone oil lubricated syringes are caused by displacement of the silicone oil from between the plunger and barrel during storage.

The much higher glide force values and more erratic glide force profiles are attributed to migration of the silicone oil into the surfactant solution during storage.

Figure 5 shows the average break-loose and gliding force values for each of the nine experimental conditions. Note that both FB and FG increase markedly with storage time for the silicone oil lubricated syringes due to the migration of the lubricant as described above. In contrast, the forces remain much more consistent with aging for the TriboLink-Si™ and TriboGlide-DS™ lubricated syringes where the lubricant is immobilised on the syringe surface.

Particle testing with surfactant

A second set of experiments was performed to investigate the sub-visible particle counts found in prefilled syringes lubricated with four different lubrication systems:

1. Baked-on silicone (b-Si), vendor-purchased
2. Silicone oil (Si), vendor-purchased
3. TriboLink-Si™ (TL), plasma immobilised silicone, applied at TriboFilm
4. TriboGlide-DS™ (TG), plasma immobilised silicone-free PFPE, applied at TriboFilm.

For each lubrication system, ten 1 mL long glass syringes were filled with a 0.05% solution of Polysorbate 80 in sterile filtered water. The filled syringes were stored at 40°C for two weeks, and then agitated on a laboratory shaker for 24 hours just prior to characterisation. The particle counts were obtained by light obscuration measurements using a Particle Sizing Systems AccuSizer 780 SIS liquid particle counter. Figure 6 shows the number of particles ≥2 µm in diameter for each of the four lubrication systems. In all cases, note that the TriboLink-Si™ and TriboGlide-DS™ lubrication systems were consistently more stable and produced significantly fewer particles than either silicone oil or baked-on silicone.

Particle testing with protein and shipping agitation

A third set of experiments was performed to investigate the sub-visible particle counts found in prefilled syringes lubricated with three different lubrication systems in the

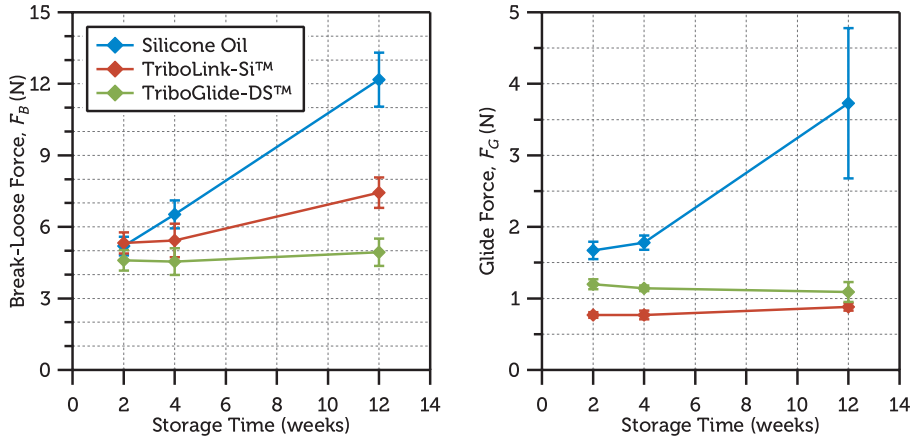


Figure 5: Average Break-Loose Force (F_B) and average Glide Force (F_G) for silicone oil, TriboLink-Si™ and TriboGlide-DS™ lubricated syringes. All samples are 1 mL long glass syringes filled with a 0.05% Polysorbate 80 solution in sterile filtered water. Sets of samples were aged for 2, 4, and 12 weeks at 40°C, and all were agitated for 24 hours just prior to characterisation. The error bars represent ± one standard deviation of the values for 10 identically prepared samples averaged to obtain each point.

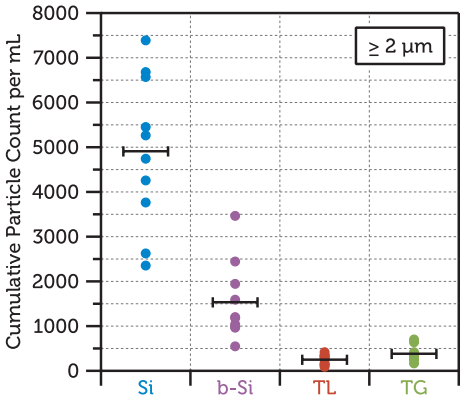


Figure 6: Particle counts for 1 mL long glass syringes lubricated with silicone oil (Si), baked-on silicone (b-Si), TriboLink-Si™ (TL), and TriboGlide-DS™ (TG). All samples were filled with a 0.05% Polysorbate 80 solution in sterile filtered water, stored for 12 weeks at 40°C, and agitated for 24 hours just prior to characterisation. The black horizontal bars represent the average value of each series.

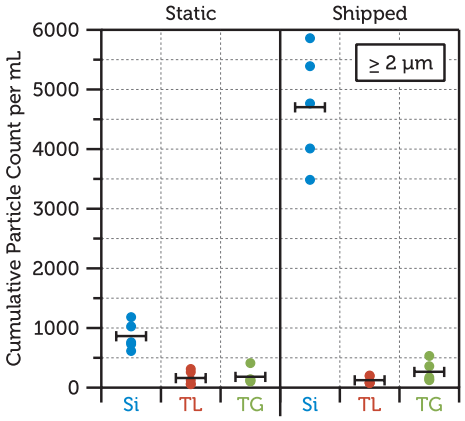


Figure 7: Particle counts for 1 mL long glass syringes lubricated with silicone oil (Si), TriboLink-Si™ (TL), and TriboGlide-DS™ (TG). All samples were filled with a 4 mg/mL solution of rHSA in pH 7.2 phosphate buffer. Half of each set of ten samples (shown on right) were overnight shipped ~2500 km. All samples were stored for four weeks at 25°C. The black horizontal bars represent the average value of each series.

presence of recombinant human serum albumin (rHSA):

1. Silicone oil (Si), vendor-purchased
2. TriboLink-Si™ (TL), applied at TriboFilm
3. TriboGlide-DS™ (TG), applied at TriboFilm.

Recombinant HSA was selected as a readily available model protein that is often used as an excipient in therapeutic protein formulations. For each lubrication system, ten 1 mL long glass syringes were filled with a 4 mg/mL solution of rHSA in a pH 7.2 phosphate buffer. Five of each set of filled syringes were shipped ~2500 km overnight by air courier, and all samples were stored at 25°C for four weeks before characterisation. The particle counts were obtained by light obscuration measurements using the same instrument described earlier. Figure 7 shows the number of particles ≥2 µm in diameter for each of the lubrication systems. Air shipment provides a real-world agitation scenario after which to characterise the different lubricants. Under static conditions, the silicone oil lubricated syringes produced more particles than either the TriboLink-Si™ or TriboGlide-DS™ syringes. After air shipment, the particle counts in the silicone oil lubricated syringes greatly increased, while those in the TriboLink-Si™ and TriboGlide-DS™ lubricated syringes remained consistently low and showed relatively little change from the unshipped control samples.

SUMMARY

Injection devices containing prefilled syringes offer many benefits for patients, while also providing product differentiation to pharmaceutical companies. Many newer injectable drugs contain therapeutic proteins, which bring additional product stability challenges due to their interactions with packaging components. Therefore the design of a proper packaging strategy is now a critical part of the product development process that requires as much attention as drug formulation and should be addressed early in the development cycle.

Syringe lubrication is often ignored during product development, which often becomes a source of significant difficulties when developing the packaging strategy for prefilled syringes. Silicone oil, the traditional industry standard syringe lubricant, has a tendency to migrate from the syringe surface into the drug product. The migration of silicone oil can detrimentally affect syringe function, and also produce sub-visible particles that can then impact the stability of biologics by forming protein/silicone aggregates.

An immobilised lubrication system can overcome the challenges described above. This article discussed two such advanced lubrication technologies for prefilled syringes:

1. TriboLink-Si™, an immobilised medical grade silicone lubricant, and
2. TriboGlide-DS™, a silicone-free immobilised perfluoropolyether lubricant.

As demonstrated above, both of these advanced lubricants offer superior performance over silicone oil and baked-on silicone lubricants, with lower and more consistent plunger forces and lower sub-visible particle loads. Standard plunger designs are compatible with both TriboLink-Si™ and TriboGlide-DS™, with no changes in material or design required to maintain container closure integrity. Both of these lubricants are compatible with glass and plastic pharmaceutical containers without limitations in size or format. These advanced immobilised lubrication systems based on TriboFilm's Atmospheric Plasma Technology effectively mitigate the risks involved with silicone oil lubrication in parenteral containers.

"Under static conditions, the silicone oil lubricated syringes produced more particles than either the TriboLink-Si™ or TriboGlide-DS™ syringes. After air shipment, the particle counts in the silicone oil lubricated syringes greatly increased, while those in the TriboLink-Si™ and TriboGlide-DS™ lubricated syringes remained consistently low and showed relatively little change from the unshipped control samples"

ABOUT TRIBOFILM RESEARCH, INC

TriboFilm Research, Inc, based in Raleigh, NC, US, is a one-of-a-kind entrepreneurial research incubator that develops advanced technologies for pharmaceutical packaging applications. With extensive knowledge and experience in surface engineering, TriboFilm has focused its research efforts on one critical aspect of parenteral packaging: device lubrication.

With support from the US National Institutes of Health, TriboFilm has developed two advanced lubrication technologies: TriboLink-Si™ and TriboGlide-DS™. TriboFilm has established worldwide patent protection on both lubrication technologies, and licenses these patents to medical device and pharmaceutical companies in targeted fields of use. Our research facility contains state-of-the-art equipment for product development, performance testing, and small-scale manufacturing. TriboFilm has all of the tools, experience, and expertise necessary to create turnkey solutions to even the most demanding of customer challenges.

"Syringe lubrication is often ignored during product development, which often becomes a source of significant difficulties when developing the packaging strategy for prefilled syringes"

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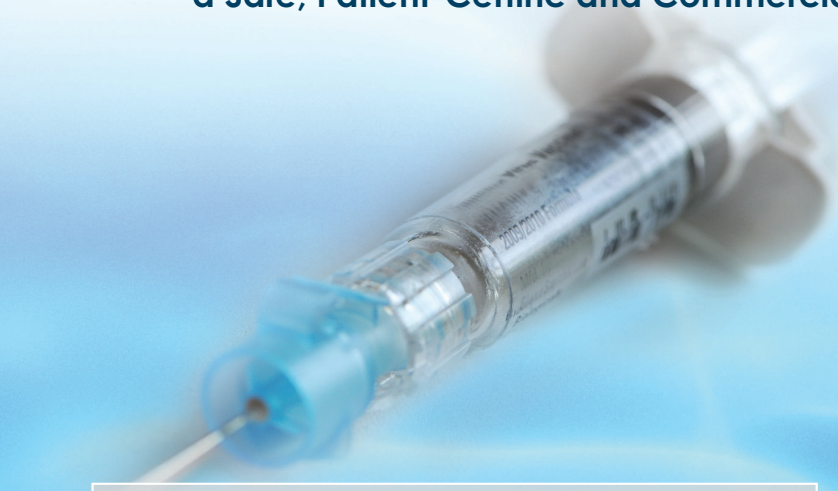

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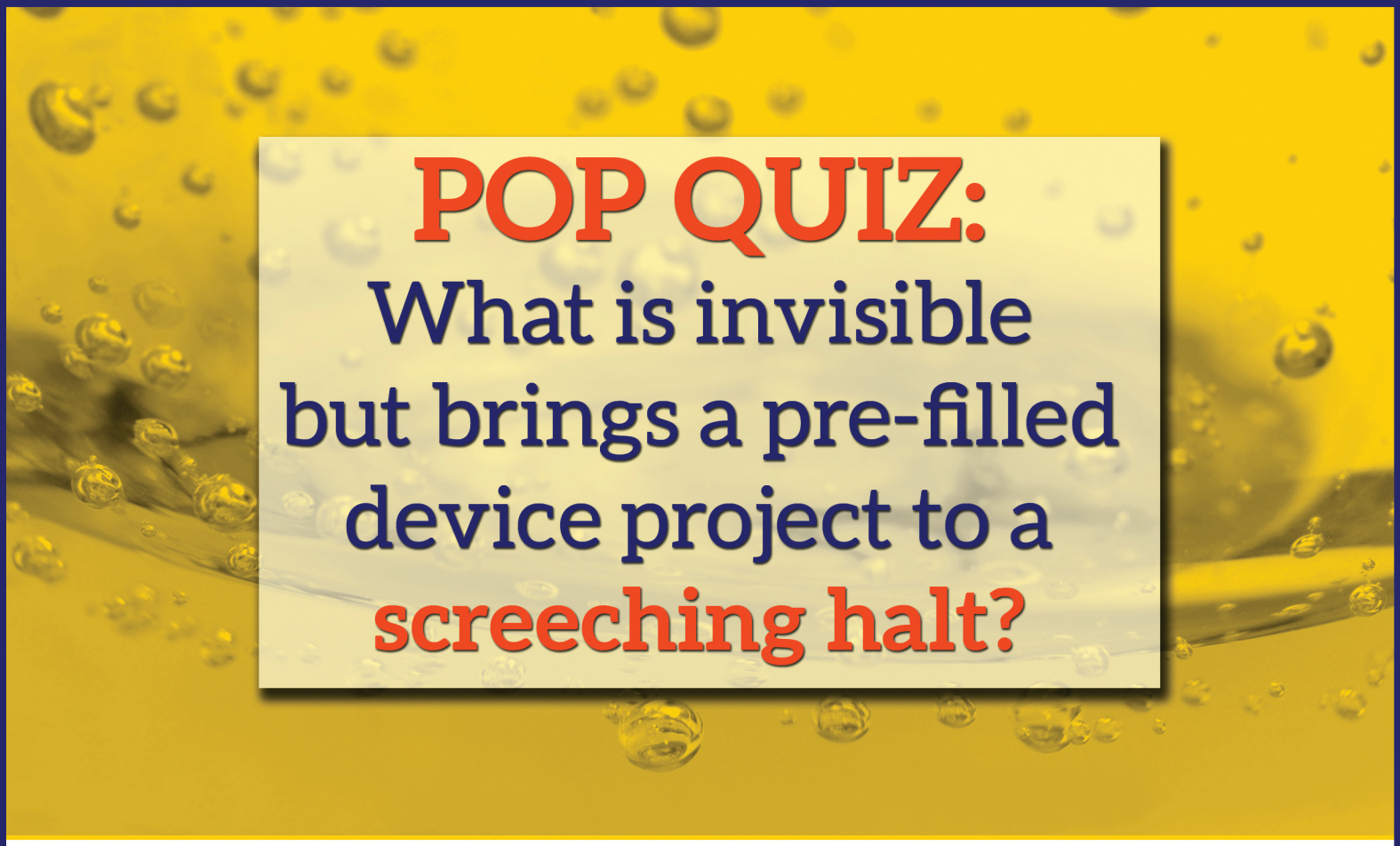

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ADVANTAGE, PHARMA: PARTNERING WITH PACKAGING & DEVICE COMPANIES EARLIER IN THE DRUG DEVELOPMENT CYCLE

In this article, Tibor Hlobik, Director, Global Marketing, Prefillable Syringe Technologies, and Kevin Cancelliere, Director, Pharmaceutical Delivery Systems Marketing, both of West Pharmaceutical Services, Inc, discuss how and why early consideration of primary packaging and drug delivery devices in pharmaceutical product development can bring benefits to all stakeholders, including patients.

Drugs, understandably, are the primary focus of research and development for pharmaceutical and biopharmaceutical companies. But with increased regulatory focus on quality in drug packaging and delivery systems, pharmaceutical manufacturers are considering the importance of containment systems ever earlier in the drug development process. Forward-thinking companies build in time for early collaboration with packaging and delivery system partners during the lengthy development process. This better positions the injectable drug to serve the needs of both the manufacturer and the patient.

> "The most successful recent blockbuster drug launches have involved specialised products that are launched to meet highly unmet medical needs in areas, including diabetes, multiple sclerosis, osteoporosis, psoriasis and schizophrenia. Each of these new drugs had one thing in common: they were launched with alternative delivery methods"

Often, one of those needs is maximising patent protection time. Research and development for a new biologic drug product can typically take as long at 15 years and cost as much as US$1.2 billion (£0.8 billion). So when the drug product reaches the market, the originator may have only a few years remaining on the patent.

That's where the expertise and experience of the packaging and delivery system partner can help – earlier in drug development – to save precious time the pharmaceutical company has for exclusive rights under patent. Typically, drug manufacturers consider drug packaging and delivery systems only during the final stages of development. If the drug product cannot be stored effectively or reacts chemically with the containment materials, or if the system does not function well with a high-viscosity drug or is not a good fit for the intended patient population, it can be a costly issue for the manufacturer. Considerations related to dosing volume, delivery technique and frequency, and type of delivered system (such as an auto injector), should all be taken into account at an early stage to ensure optimum speed-to-market and opportunity for success.

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EARLIER TESTING, BETTER RISK MITIGATION

Collaborating with a single partner with diverse expertise in primary packaging, delivery systems, custom design and analytical testing early in the drug process can help at a variety of stages. For example, packaging manufacturers that also provide analytical laboratory services can offer product recommendations for the latest alternative technologies and provide prescreen stability work early in the process to ensure that the containment materials do not react with the drug product.

Many biologics, by their very nature, do not respond well to glass containment, which can result in higher levels of inorganic leachables, protein aggregation or the risk of glass delamination. To achieve the best possible patient outcomes, pharmaceutical companies developing complex and sensitive biologic or biosimilar injectable therapies must consider how the drug product will interact with the primary container, the delivery system and the patient to help ensure compliance to prescribed regimens and loyalty to specific brands. The most successful recent blockbuster drug launches have involved specialised products that are launched to meet highly unmet medical needs areas, including diabetes, multiple sclerosis, osteoporosis, psoriasis and schizophrenia. Each of these new drugs had one thing in common: they were launched with alternative delivery methods.

By partnering with a component manufacturer early in the drug development process, pharmaceutical manufacturers can identify and mitigate many of the risks associated with poor containment selection. Flexible containment solutions that use the same materials for drug contact, but in a variety of configuration options that aid in stability and delivery from discovery through commercialisation and drug lifecycle management, may help achieve better patient outcomes.

ENSURE DRUG STABILITY AND LIMIT LEACHABLES FORMATION ASSOCIATED WITH CLOSURES

Every company involved in packaging injectable products, especially sensitive and biologic drugs, is concerned about long-term stability and the impact of potential extractables on drug quality and patient safety. The most frequently asked question is, "What is the acceptable level of leachables over the shelf life of my product and associated risk to the patient population?"

Figure 1: NovaPure® plungers with FluroTec® film provide high reliability for prefilled syringe systems.

By applying barrier films to stoppers, plungers and cartridge components, an elastomer closure's performance can be improved. Such films can help reduce the risk of interaction between the drug and container closure system and protect the drug from contamination. FluroTec® film provides an effective barrier against organic and inorganic extractables, minimising interaction between the drug and the closure while maintaining container closure integrity. The fluoropolymer film reduces drug product absorption and adsorption, an important benefit for maintaining the strength and shelf life of most drugs. In addition, the low surface energy of FluroTec film, in combination with a lubricious coating, such as B2-Coating, eliminates the need for added free silicone oil on the component, eliminating one potential source of particulate contamination.

A NEW WAY TO MEET INCREASING QUALITY REQUIREMENTS AND DEVICE COMPATIBILITY

Quality by Design (QbD) promotes understanding of the product and manufacturing process starting with product development. When designing and developing a product using QbD principles, manufacturers must define desired product performance and identify Critical Quality Attributes (CQAs). The product and process is then designed to meet those product attributes, which leads to understanding the impact of material attributes and process parameters on the CQAs and identification and control of sources of variability. As a result of this knowledge, a manufacturer can continually monitor and improve its manufacturing process to assure consistent product quality.

As market demand for higher quality and patient need for self-injection with auto injectors have evolved, demand for a high-quality plunger has grown. Using QbD principles, West developed its NovaPure® plunger (Figure 1) with FluroTec film for prefilled syringe systems to provide high reliability for break-loose and glide force, dimensional accuracy, sub-visible and visible particulate control, and low parts per million (ppm) defect attributes. The optimised functional performance for NovaPure plungers can provide improved rate of injection times and consistency when used in conjunction with 1 mL long syringes and an auto injector system.

POLYMERS GAINING ON GLASS

Examination of potential fundamental incompatibilities between drug formulations and container closure systems, has led manufacturers to explore and adopt alternative primary container materials such as cyclic olefin polymers (COPs). These can help assure optimum stability during a drug product's shelf life.

Cyclic olefin polymers may offer a safer, more effective and reliable alternative to traditional glass. Because COPs can be moulded to a variety of shapes, they can provide adaptability to different administration forms (e.g. infusion to injection to self-administration) throughout the product's lifecycle. Such choices early in development may aid decisions later in the manufacturing cycle. COPs offer improved dimensional tolerance and design flexibility, so innovative container/device combinations can be considered to help optimise overall system design based on the needs of the patient.

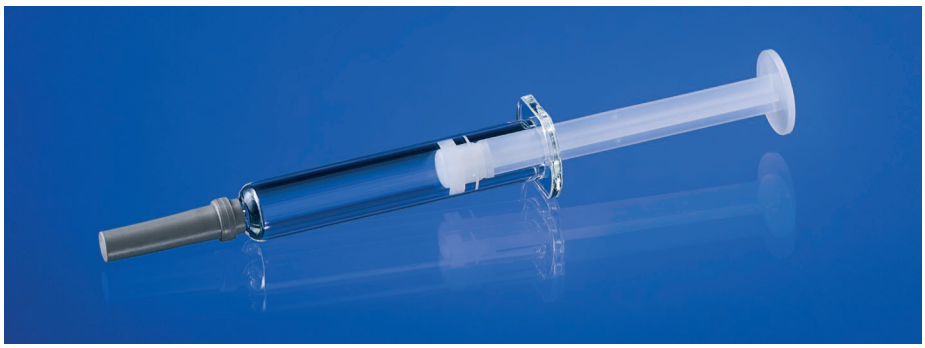

Figure 2: The Daikyo Crystal Zenith® 1 mL Insert needle syringe.

Companies challenged with multiple containment needs for drug lifecycle management strategies can work closely with the partner to match technology, collaborate during development and ensure primary container compatibility with the drug and device for best patient outcomes. Many biotech and sensitive drug products have unique requirements, and polymer systems provide key solutions for patient safety and compliance. There are a variety of products on the market that can help mitigate these risks, including insert needle prefillable syringes, such as the Daikyo Crystal Zenith® 1mL Insert needle syringe (Figure 2), which may be required for a drug product with metal and silicone oil sensitivities.

Another consideration in this process is the need to integrate primary containers into drug-device combination products. As patients take a more active role in their individual healthcare, and the administration of injectable drug products moves from hospital to in-home setting, there is a greater need to provide easy-to-use delivery systems or combination products that assure safe and reliable self-administration. This may include the use of prefillable syringes, which help in dosing accuracy and minimise errors when compared with a vial and disposable syringe format.

AUTO INJECTORS, CARTRIDGE-BASED SYSTEMS HELP PATIENTS COPE

There has also been an increase in the use of disposable auto injector systems, which aid dosing convenience, and may help reduce patient fear because they include safety features that hide the needle before and after injection.

Another trend allowing for even greater patient convenience is the use of cartridge-based systems. These may include pen injectors for frequently administered products, as well as large-volume electronic wearable injector delivery systems that can offer either less frequent administration or conversions of products from intravenous to subcutaneous administration.

West's SmartDose® electronic wearable injector is designed to deliver higher fill volumes of injectable drugs over an extended period of time, making it easier for patients to self-administer medication and encouraging compliance with prescribed treatments.

EARLY COLLABORATION, MORE OPPORTUNITIES

Between 2003 and 2014, the number of top selling biologic drugs has grown from one product to five. Biologics and biosimilars have seen continued growth at a pace that exceeds other drugs in the market and in the pipeline. Through 2018, biologics spending will continue to grow faster than medicines overall, driven by innovation.

It is important to note that biologics make up roughly one-third of the late-stage drug pipeline. Companies developing these specialised drugs can hedge their bets for success by selecting a packaging partner that can accommodate the complexities biologics sometimes introduce to the process.

West is proud to partner with our customers to anticipate their packaging and drug delivery needs and bring them value-added solutions to remain competitive in today's complex healthcare landscape.

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> "The most frequently asked question is 'What is the acceptable level of leachables over the shelf life of my product and associated risk to the patient population?'"

ABOUT THE AUTHORS

Tibor Hlobik, Global Director, Marketing for PFS Technologies

Tibor Hlobik has worked within the pharmaceutical packaging industry for over twenty-five years in areas of research and development, corporate quality, technical services and marketing primarily at West Pharmaceutical Services. He has extensive knowledge and experience with prefilled syringe systems and cartridge based solutions, and related technologies. Currently in his role as Global Director, Marketing for PFS Technologies at West Pharmaceutical Services, Tibor is responsible for defining new market requirements, launching new products, supporting business development plans, and overall execution of global marketing strategies for West.

Kevin Cancelliere, Director of Marketing, Pharmaceutical Delivery Systems

Kevin Cancelliere joined West Pharmaceutical Services in January 2013 as Director of Marketing, Pharmaceutical Delivery Systems. Kevin brings almost thirty years of broad operational and strategic marketing and sales experience to this position. He comes to us from Vicept Therapeutics where he was Senior Director, Project Management for an investigational drug for the treatment of Rosacea. Prior to Vicept, Kevin was the Senior Director, US Marketing at Wyeth Laboratories. Kevin holds a BS in Biology from De Sales University and a Masters in Biochemistry from Thomas Jefferson University.

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THE EVOLVING & CHALLENGING REGULATORY LANDSCAPE FOR COMBINATION PRODUCTS

In this piece, Alice Maden, PharmD, Global and Regional Regulatory Affairs Manager, and Kathleen O'Sullivan, MS, RAC, Worldwide Director, Regulatory Affairs, both of BD Medical, take the practical example of a drug product filled in a BD Hypak™ glass prefillable syringe to describe how the worldwide regulatory environment of combination products has rapidly evolved. BD's Regulatory Affairs team has adapted their support offerings and customised solutions to assist customers from the pharmaceutical and biotechnology industry to sustain this major change.

During the past two years, the pharmaceutical industry has received clear signals from regulatory authorities indicating that worldwide regulatory expectations on container closure systems and delivery systems for parenteral medical products are rapidly evolving. Global examples are seen in the US, EU and Japan regulations.

United States

In the US, the Final Rule for Current Good Manufacturing Practices (cGMPs) for Combination Products was published by the FDA on January 22, 2013 and issued under 21 CFR Part 4. Industry had been waiting for several years since the initial publication of the proposed rule by the Agency in 2009, which had first been drafted in 2004. In 2013 with the issuance of the final rule, FDA expected the industry to have completed implementation by July 22, 2013. The FDA's goal in issuing the rule was to enhance consistency of regulatory requirements for these types of products, as well as to encourage innovation.

Within the new guidance was the concept of a 'streamlined approach' to the application of the good manufacturing practices or quality system regulation (QSR). Under the rule, the requirements in sections 210 and 211 of 21 CFR were applicable to combination products containing a drug, while in part 820 the quality system regulations were applicable to combination products containing a device. Streamlining meant it was unnecessary to include all provisions of both systems, but enabled the leveraging of the necessary elements required from each system of cGMPs and QSR. One system of cGMP /QSR requirements would apply for a single entity or co-packaged combination product using elements from both 21 CFR parts 210 and 211, and part 820 for drug/device combination products. An example of a combination product that would leverage both drug and device GMPs/QSR would be a drug contained in a prefilled syringe.

At the time of the publication of the final rule, FDA recognised that industry would have some unanswered questions related to the rule and had plans to issue several other guidance documents to meet these needs and address any gaps. These additional guidances would include clarification on topics, such as human factors studies, post market changes, stability, retention samples, and information required for prefilled syringes, in addition to the applicable standards, and others specifically related to combination products. Subsequently several guidance documents or draft guidance documents were issued including the following:

- 01/2015 Guidance for Industry and FDA Staff: Current Good Manufacturing Practice Requirements for Combination Products, Draft Guidance
- 06/2013 Technical Considerations for Pen, Jet, & Related Injectors Intended for Use with Drugs & Biological Products
- 04/2013 Glass Syringes for Delivering Drug and Biological Products: Technical

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Information to Supplement International Organization for Standardization (ISO) Standard 11040-4

- 01/2013 Submissions for Post-approval Modifications to a Combination Product Approved Under a BLA, NDA, or PMA

The industry is facing several complexities today, such as how to manage products that have been in the market place for many years prior to combination product regulations and prior to the device amendments of 1976. Products in some cases have existed on the market for up to fifty years, were designed according to the practices of their time and have been proven to be safe and effective products. A troubling question facing some manufacturers is whether or not these products can be manufactured according to today's newer standards, and successfully pass the required tests using current technologies.

Another area requiring clarification is the issue of change control of "legacy" products on the market for many years. Changes would naturally be expected to conform to today's standards. However, manufacturers' ability to do this again comes into question as do the implications of not changing anything because of the knowledge that such products may not meet newer requirements, i.e. requirements that were not around at the time the product was designed initially. This avoidance of change may impede the desire to enhance the product.

Additionally, there is the question of how inspections would occur on older marketed products and the expectations of the regulators during such inspections. As the combination product regulations and additional guidance evolves in the US, manufacturers of combination products are now facing these conundrums along with a need for clarification on matters related to reserve samples, calculation of yield, human factors, stability testing and design controls for combination products.

Europe

In Europe, further to the PIP breast implant debacle, new proposals [1] for the regulation of medical devices were published by the European Commission (EC) in September 2012. These two draft regulations are currently under discussion at the EC and the European Parliament and are expected to replace the existing three medical device directives in the future. The main purpose of these new regulations is to ensure safer medical devices and to provide more transparency in order to regain users' and patients' trust.

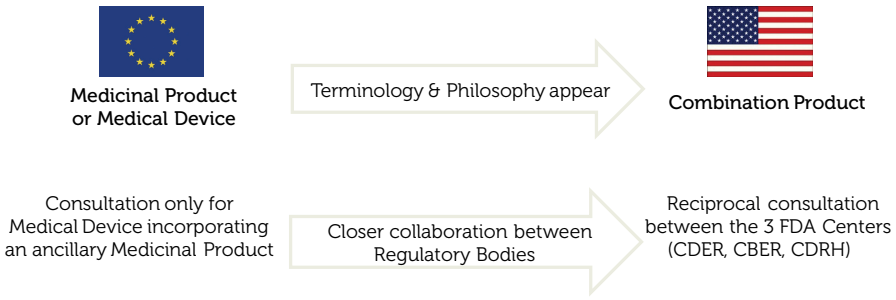

Figure 1: The philosophy of combination products, which has been established in the US for several years, is gaining acceptance in Europe.

Among the numerous pillars of this updated regulatory framework, most of them are specific to the medical device industry, such as better qualification of Notified Bodies, unannounced audits by Notified Bodies for manufacturers of CE-marked medical devices, or unique device identification (UDI) systems for an enhanced traceability. **More specifically, in the draft regulation on medical devices, some parts are more focused on combination products with the following changes: The term "combination product" which has been used for a long time in the US appears for the first time in Europe.**

Using an example of a drug product filled into a BD Hypak™ glass prefillable syringe, it is clear in the language of "*sections 3.9. Final provisions (Chapter X)*", "*Whereas (9)*" and "*Legislative Financial Statement section 1.5.4. Coherence and possible synergy with other relevant instruments of the draft regulations*" that this constitutes a combination product.

Also, in the framework of improved synergies with other legislations including medicinal products, the draft regulation focuses on compliance of drug/device combination products with the list of essential requirements governing medical devices in Europe, as clearly indicated in "Section 3.9 Final provisions (chapter X)". This requirement is already applicable today but every European institution agrees that "compliance with this requirement is not currently verified as part of the authorisation process for the medicinal product".

The practical consequence for manufacturers of drugs in prefilled syringes is that they will have to provide clear demonstration of the compliance of the syringe part of their combination product with the applicable sections of this list of essential requirements.

This represents an important step forward in the growing philosophy of combination products in Europe (Figure 1).

Japan

In the third geography of the ICH Organisation, the Japanese Pharmaceutical Affairs Law (PAL) was updated in November 2014 to include a new, adapted regulatory strategy option for combination products.

In the past, pharmaceutical companies planning a submission for the Japanese market consisting of a drug product filled in a BD Hypak™ glass prefillable syringe had to file two separate submissions. A medical device application including the syringe information had to be submitted to the Pharmaceuticals & Medical Devices Agency (PMDA) for review. In addition, a second file focused on the drug product and referencing the medical device approval, once available, had to be submitted separately to the Ministry of Health Labour and Welfare (MHLW) for review.

As of November 2014, a new option became possible allowing a combined approach whereby pharmaceutical companies submit to the MHLW one combination product application including both the drug product and medical device information together. This is yet another sign that the combination product trend is strengthening.

REGULATORY AFFAIRS AT BD

BD's Regulatory Affairs Team, which has a breadth of experience in providing comprehensive, informed regulatory support and consultation, aligns its regulatory offering while meeting the evolving expectations of its customers.

This support is based on two central deliverables:

- The letter of authorisation (LOA), which we deliver to customers for the registration of our BD Hypak™ glass prefillable syringe and other container closure systems in the US, Canada and Australia.
- The Technical Dossier, which we deliver to our customers for registration in other territories.

Other Geographies

Due to the recent changes and evolving requirements from health authorities regarding container closure and delivery

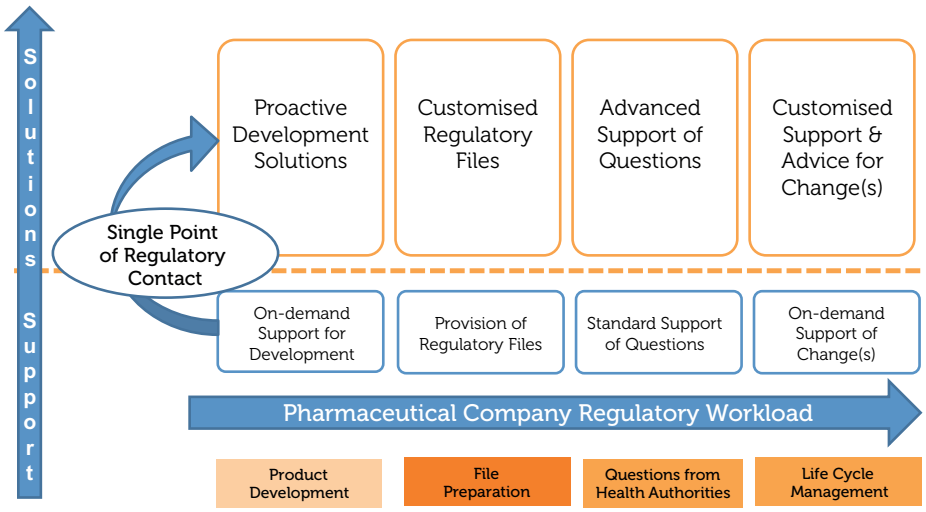

Figure 2: BD's comprehensive set of agile, customised regulatory affairs solutions, encompassing early development through life cycle management.

systems, BD's Regulatory Affairs Team has more recently launched several initiatives in alignment with this evolving environment.

Based on a case-by-case discussion between our customers and a single point of regulatory contact from our team, we are in a position to leverage global regulatory expertise to support and collaborate with our customers, and help them not only attain their registration goals, but provide ongoing consultation and services throughout the product lifecycle.

A COMPREHENSIVE & GRADUAL OFFER

BD's offering is comprehensive and gradual, from *ad hoc* requests to proactive case-by-case collaboration and partnership. To support our customers in their product development and filing phases, we have developed a regulatory dossier, a Customised Common Technical Dossier (CTD) for Customers designed to fit into the format and content of regulatory submissions, offering the convenience of integrating our "ready-to-use" document into their submission, saving time and effort and potentially shortening approval timeline.

This solution, when provided to our customers, has proven to be invaluable, resulting in fewer questions from the health authority and no blocking point related to the BD Products embedded. This success is further evidenced by increasing requests for this offer from our customers. Additionally, BD – recognising customers' challenges when purchasing components for their combination products – proactively sought out advice on its Customised CTD by going beyond the usual barriers of a supplier of components. We presented the Customised CTD principle to the UK MHRA during a Scientific Advice meeting in November 2013. According to the MHRA: "The scope of data presented has been considered as a good supportive data package."

Related to this customised CTD is the customised follow-up consultation provided in the event of questions from European health authorities. A single point of regulatory contact supports the pharma customer in case of any questions from the health authority with respect to BD products, in a timely, responsive manner. Further, this customised solution will be useful to customers who wish to launch or modify an existing product on the European market. It is particularly valuable for the entry of biosimilars to the European market as this is an area where it is critical to be expeditious and "right the first time". In this area of biosimilars, customised filing support using the skills of an experienced regulatory group can make a valuable difference in navigating the complex regulatory environment.

In Japan, we are in a position to provide our worldwide customers entering this market with regulatory dossiers for the BD components they use. Our offer has been evolving in alignment with the new law issued in November 2014 and we now provide customers with device sections of combination product regulatory files, among other available services. This device section is included in the customer's combination product application and the complete dossier is then submitted to the MHLW for review and approval.

For a mature product, pharmaceutical companies may want to switch to a more advanced container closure system or to an additional presentation, such as the addition of an auto injector to an existing marketed prefilled syringe. Whether this lifecycle management activity is intended to maintain or gain share of sales, to improve product technology, or to increase patient compliance, our Regulatory Affairs team has developed lifecycle management tools to simplify such a switch by clarifying the expected regulatory impact and by providing the expertise to aid a smooth transition.

Container closure and delivery systems are becoming a pillar of combination product development. In the past, Pharmaceutical Companies typically did not consider available container closure and delivery system options before Phase III clinical studies, evolving health authority expectations are now pushing for an integrated approach starting at a very early stage. As highlighted, BD Regulatory Affairs has developed a comprehensive set of agile, customised solutions, encompassing early development through life cycle management (Figure 2), to streamline and facilitate timely approvals or product maintenance for our customers, thereby supporting their marketing and launch strategies.

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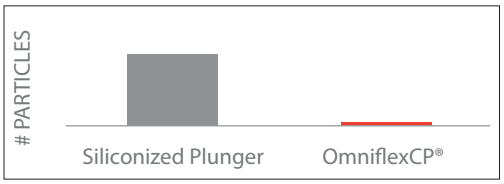

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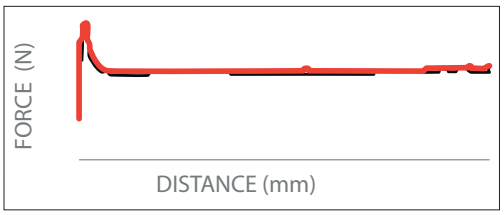

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DATWYLER

OPTIMISATION OF SYRINGE PERFORMANCE FOR OCULAR INJECTIONS & BEYOND: IMPACT OF SILICONE OIL

In this piece, Susan M Dounce, Senior Manager, Business Development & Innovation, Injection Systems, Datwyler Pharma Packaging; and Anil Kumar Busimi, Head of Global Product Management Syringe Business, SCHOTT Pharmaceutical Systems, describe the increasingly significant role of prefilled syringes in the delivery of ocular therapeutics, including in particular biologics, and show how the combination of silicone-free coated plungers with baked-on silicone syringe barrels minimise silicone-oil-based subvisible particles and enable the highly consistent delivery forces required in ophthalmic applications..

In recent years, ophthalmic drug delivery has been recognised as having some of the most significantly unmet packaging and delivery needs of any injectable drug market segment. Ocular injections often require very small, precise dose volumes to be administered in a smooth, controlled manner to a precise location in the eye without the introduction of air bubbles or foreign particulate matter such as silicone oil.

The vast majority of these injections are still aseptically prepared from vials into siliconised disposable syringes via a multi-step process that can introduce dose inaccuracy, sterility risks, and silicone oil droplets. While these challenges can potentially be addressed by the use of appropriately designed prefilled syringes, such syringes for ocular injections are only newly emerging.

Of particular concern in ocular injections is the presence of silicone oil droplets and numerous studies have confirmed that silicone oil from disposable syringes is indeed introduced into the eye during injection.[1-3] In one study, affected patients were monitored for reactions or complaints of floaters in their fields of vision and while no adverse clinical events were noted, there is general consensus that the situation should be avoided.[4] Kocabora *et al* state, "The functional and clinical consequences of intravitreal silicone oil droplets are unknown, but their occurrence could be avoided by using new-generation prefilled syringes that do not have an internal silicone coating." [4] Furthermore, studies have shown that low-molecular-weight components of silicone oil can cause acute ocular toxicity in animal models.[5]

As prefilled syringes begin to gain traction as the preferred delivery mode for ocular injections, silicone oil will be a concern, not only due to the potential for direct complications related to injected droplets, but also from the perspective of safety and efficacy of the drug during long-term storage in contact with siliconised syringe components.[1] The high packaging demands of the ophthalmic injectables market are reinforced by the fact that the top two drugs, Lucentis (ranibizumab) and Eylea (aflibercept), which together represented

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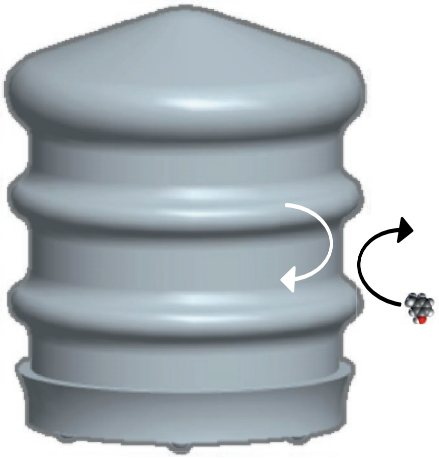
99% of the 2014 market by revenue and 60% of the market by sales volume, are both biologics. Additionally, the development pipeline for injectable drugs to treat various ophthalmic indications, especially macular degeneration, contains numerous new biologic entities.

The safety and efficacy of biologic drugs can depend sensitively on the exact chemical make-up and three-dimensional conformation of the protein. Interactions with primary packaging can lead to chemical and/or conformational changes and degradation and/or aggregation, possibly rendering the therapeutic protein ineffective or even immunogenic. The adsorption and desorption of biologics at aqueous-silicone oil interfaces can cause non-native structural conformations to arise and protein aggregates to form.[6-7] The nucleation of proteins at silicone oil particle interfaces is a known degradation pathway for some therapeutic biologics and can result in diminished drug efficacy.[8] Thus, for ocular injections, in order to minimise complications and to ensure the safety and efficacy of the drugs, the reduction or elimination of free silicone oil is a key value-driver in drug delivery technology development.

Injections into the eye call for a high level of physician control in order to deliver precise doses to precise locations.[9] It is therefore desirable for any syringe system used for ocular injections to have a smooth delivery force profile as the drug is being dispensed. However, the overall usability of disposable and prefilled syringes alike is often affected by a stick-slip phenomenon as the syringe plunger traverses areas of the barrel with lower or higher levels of lubrication. During plunger placement and over time as a siliconised plunger is stored in contact with a siliconised syringe barrel, silicone oil can migrate,[10] resulting in a non-uniform distribution of lubricant at the plunger's rest position. This in turn can lead to glide forces that can oscillate from high to low during injection. Stick-slip behaviour is particularly undesirable in precision applications such as ocular injections and reducing or eliminating silicone oil is one way to mitigate this problem.

Prefilled syringes can be designed to address the cleanliness, compatibility, and usability challenges associated with ocular injections but their performance depends on the function of multiple components within the prefilled syringe system. Omniflex-coated plungers, with their lubricious fluoropolymer barrier coating, eliminate the plunger as a source of migrating silicone oil thus enabling long-term compatibility with biologic drugs and highly consistent delivery forces. The syriQ® InJentle syringe, with baked-on silicone, a novel fluid path design, and thin needles, also results in reduced silicone levels, superior compatibility and high-precision drug delivery. Together, OmniflexCP® and the syriQ® InJentle syringe provide an integral solution to the many challenges associated with ocular injections.



No Siliconisation
- ✔ Fixed, Lubricious Omniflex Coating
- ✔ Low Coefficient of Friction

Ultra-Low Subvisible Particle Levels
- ✔ Elimination of siliconisation - the largest source of subvisible particles

Superior Chemical Compatibility
- ✔ Total Coating Coverage
- ✔ Inert Barrier

Highly Consistent Delivery Forces
- ✔ Fixed, Lubricious Omniflex Coating
- ✔ Optimised Rill Diameters
- ✔ Undercut Trim Edge

Figure 1: Key differentiators of OmniflexCP®.

DATWYLER OMNIFLEXCP®: LUBRICIOUS, FLUOROPOLYMER BARRIER COATED PLUNGERS

Omniflex Coated Plungers (OmniflexCP®) are bromobutyl prefilled syringe plungers with a proprietary, thin, flexible, inert fluoropolymer barrier coating that imparts a low co-efficient of friction without the need for siliconisation (Figure 1). The coating is applied in a two-step process. First, the plungers are loaded into a stainless steel drum and the proprietary fluoropolymer film is applied by a tumble spray coating process. The coated plungers are then subjected to a thermal post-treatment step to covalently bond the coating to the bromobutyl rubber substrate and to form a smooth, continuous fluoropolymer film.

Due to the line-of-sight nature of the spray coating process, the entire plunger surface is coated except for the interior of the plunger-rod cavity. This spray coating process is one of the keys to OmniflexCP®'s superior compatibility and performance. The total coverage of the plunger by the OmniflexCP® spray coating is in contrast to the partial coverage of most film-coated plungers and has the added benefit of providing a complete barrier film on top of every rubber surface that is in contact with the syringe barrel or drug product. The total coverage of the lubricious OmniflexCP® coating also eliminates the need for partial siliconisation of the plunger rills.

The OmniflexCP® coating is designed to reduce extractable levels (especially metal ions) from the base rubber and also to prevent the API or formulation components from interacting with the elastomer. Omniflex coated closures are widely used throughout the industry for packaging small-molecule drugs that can be absorbed into uncoated elastomers or that may lose potency by reaction with the rubber. The coating is lipophobic / oleophobic and

> "The high packaging demands of the ophthalmic injectables market are reinforced by the fact that the top two drugs, Lucentis (ranibizumab) and Eylea (aflibercept), which together represented 99% of the 2014 market by revenue and 60% of the market by sales volume, are both biologics"

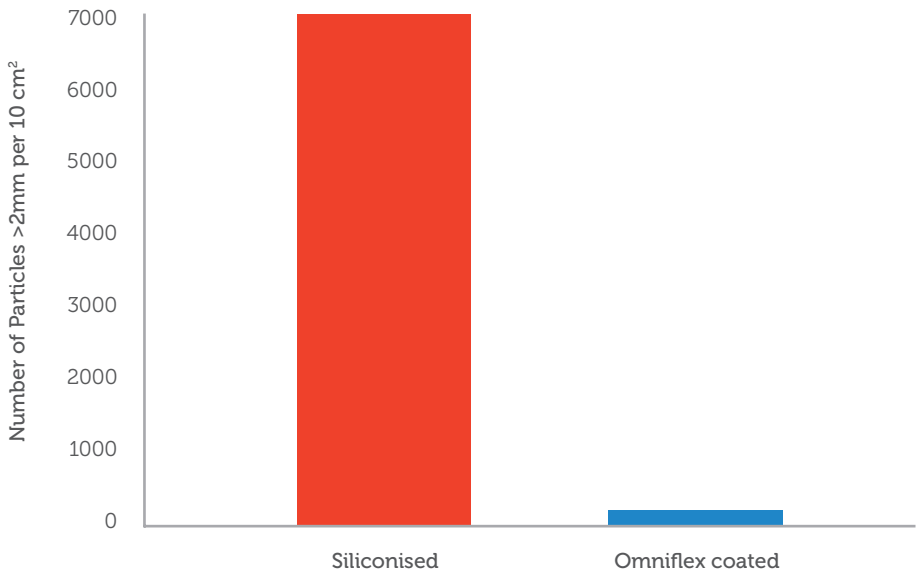


Figure 2: Number of particles greater than 2 µm in size, normalised to 10 cm² of rubber, for elastomeric closures that have been siliconised with a low viscosity (350 cSt) silicone oil (red bar) versus elastomeric closures that have been Omniflex coated (blue bar). Particle counts are determined in accordance with the method outlined in ISO 8871-3.

therefore is an excellent barrier for lipid-based or oil-based formulations. In addition to the barrier properties, the lack of siliconisation, very low subvisible particle (SbVP) levels, and highly consistent delivery forces associated with the OmniflexCP® coating make these plungers inherently well suited for biologic drug packaging or for any applications that require high precision drug delivery such as ophthalmic injections.

In a study published in the Journal of Pharmaceutical Sciences, Felsovalyi *et al* demonstrated that when it comes to silicone oil migrating into a prefilled syringe formulation, the plunger can be the larger source of free silicone as compared with the barrel – even despite the fact that more silicone oil is applied to the barrel.[11] Thus, when working to reduce silicone levels and overall SbVP levels from prefilled syringe systems, it is important to consider contributions from both the barrel and from the plunger.

Traditionally, elastomeric prefilled syringe plungers are siliconised with a 350-1000 cSt silicone oil in order to prevent sticking, to enable machinability, and to optimise syringe delivery forces. These low viscosity silicone oils are associated with high levels of SbVPs. Figure 2 shows the number of SbVP's greater than 2 µm in size per 10 cm² of rubber surface area for a 350 cSt silicone oil (grey bar) *versus* an Omniflex coating (blue bar). More than one order of magnitude decrease in SbVP levels is realised for the Omniflex coating compared with siliconisation.

> "Injections into the eye call for a high level of physician control in order to deliver precise doses to precise locations.[9] It is therefore desirable for any syringe system used for ocular injections to have a smooth delivery force profile as the drug is being dispensed"

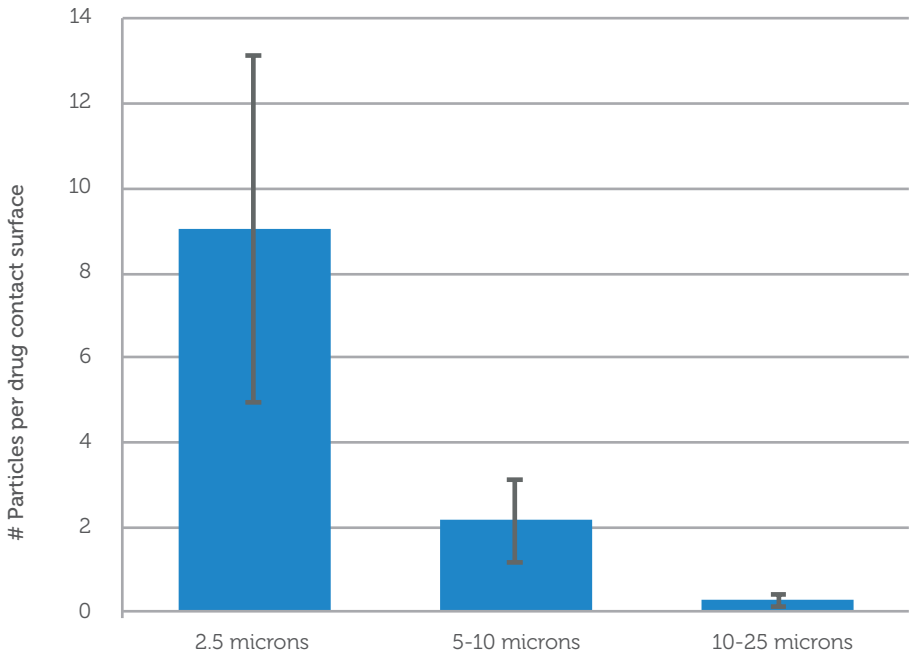


Figure 3: Number of particles per drug contact surface area of a 1 mL long syringe plunger for OmniflexCP®. Particle counts are determined in accordance with the method outlined in ISO 8871-3.

The reason for the significant reduction in particle levels with OmniflexCP® is the absence of silicone oil-based SbVPs. This has been demonstrated by the investigations of Felsovalyi *et al.* [11] The silicone oil-based SbVP levels of OmniflexCP®, a siliconised plunger, and a film-coated plunger were compared. OmniflexCP® was associated with zero silicone oil-based SbVPs while significant levels detected with the other two plungers. The overall SbVP levels of OmniflexCP® per drug contact surface of a 1 mL long plunger are shown in Figure 3. The lack of siliconisation allows SbVP levels as low as 12 particles / syringe plunger in the range of 2-25 µm (according to ISO standard 8871-3), to be realised.

SCHOTT SYRIQ® INJENTLE – INNOVATIVE STAKED-NEEDLE SYRINGE

The syriQ™ InJentle prefillable syringe is designed to meet the growing demands of delivery systems for sensitive drugs and safer, more comfortable injections. syriQ® InJentle (Figure 4) consists of a glass barrel and a newly designed syringe cone with a fluid path made of rubber (a component also manufactured by Datwyler), including

a staked-in needle. A "pinch seal" keeps the fluid path closed during storage. This newly designed closure prevents the drug from coming into contact with the metal needle or the adhesive. As a result, the drug cannot interact with these substances. The special design of the glass barrel also eliminates the use of a tungsten pin during the glass forming process. Tungsten pins are typically used to keep the fluid path open at the nozzle end of the syringe during the glass forming process. Residual tungsten can migrate into the drug product and lead to unwanted interactions or protein aggregation.

The syriQ® InJentle barrel has baked-on silicone, which significantly reduces the interaction between the drug and the silicone while maintaining syringe functionality. syriQ® InJentle syringes are designed so as to ensure the needle does not stick into the tamper evident needle shield, preserving the needle's sharpness. This, combined with high-tech needle siliconisation, leads to needles with a low penetration force. In fact, syriQ® InJentle syringes can be offered with thin needles – up to 32 gauge. This makes injections less painful for the patient. syriQ® InJentle includes many special features and offers advantages for ophthalmic injections. This innovative syringe is still delivered in standard nests and tubs and can be filled on standard filling lines.

Drug Friendly

- Tungsten-free
- No contact between drug and needle/adhesive*
- Baked-on silicone (optimal break-loose, gliding forces)*
- Low residual volume*

User Friendly

- Tamper-evident closure
- Thin needles*
- Needle not in contact with needle shield*
- Easy-to-use*

*Benefits for ocular inJections

Figure 4: The syriQ® InJentle syringe. The image on the right depicts the elastomer fluid pathway (dark grey) which is also produced by Datwyler. The pinch seal (yellow) is automatically disengaged upon pulling the rigid needle shield to break the tamper-evident ring.

COMBINED PERFORMANCE OF OMNIFLEXCP® & SYRIQ® INJENTLE SYRINGE SYSTEM

Figure 5 shows typical delivery force profiles (100 mm/min) of the syriQ® InJentle syringe (1 mL long, 29 guage, ½" needle) in combination with traditional siliconised plungers (red curve) and in combination with OmniflexCP® (blue curve). The syringes, which are lubricated with baked-on silicone, were water-filled and aged at 40°C, 75% relative humidity for 105 days. The siliconised plungers are a standard ISO 1 mL long design, in Datwyler's FM257 bromobutyl compound (the same base compound as used with OmniflexCP®), siliconised with a 30,000 cSt silicone oil. The open circles and squares in Figure 5 represent the mean break-loose and glide forces, respectively, averaged over 27 samples. These experiments demonstrate that the OmniflexCP® design and the fixed, lubricious Omniflex coating together result in highly consistent forces as compared to siliconised plungers.

The Finite Element Analysis (FEA) simulations in Figure 6 (next page) show the impact of the different plunger designs on the radial stress profiles. In the OmniflexCP® design (right) the diameters of the second and third trailing rills have been slightly decreased as compared with the ISO standard (left). Additionally, the trim edge is undercut on the OmniflexCP® design so that it is no longer in contact with the barrel.

Despite the fact that the trim edge is not intended to be a sealing rill, it is a significant contributor to the frictional forces for the ISO standard design. The undercut trim edge and the reduced rill diameters in OmniflexCP® help contribute to the optimum delivery forces in the blue curve in Figure 5.

Beyond the plunger design, the lack of siliconisation of OmniflexCP® is key in eliminating the stick-slip behaviour that is typical of most plungers. Comparing the red

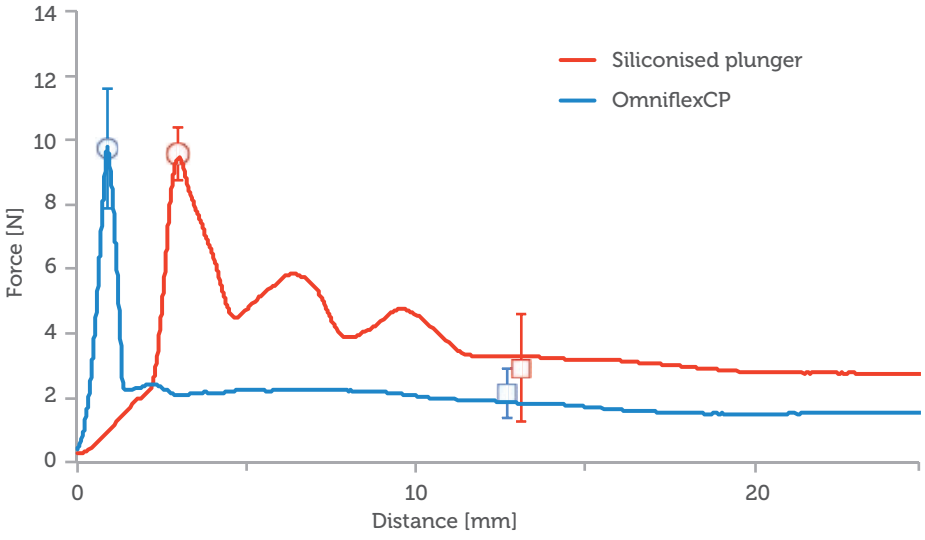


Figure 5: Typical delivery force profiles (100 mm/min) for 1 mL long syriQ® InJentle syringes (29 G, ½" needle) in combination with siliconised plungers (red curve) and OmniflexCP® (blue curve). Syringes were water-filled and aged 105 days at 40°C, 75% R.H. Open circles and squares represent the mean break-loose and glide forces respectively, averaged over 27 samples.

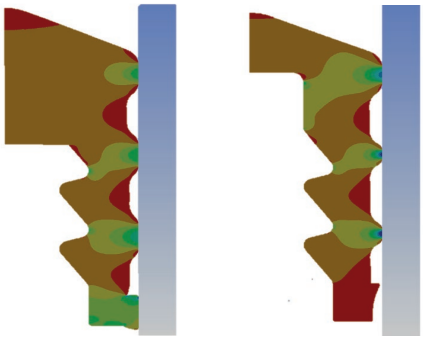


Figure 6: Radial stress profiles for ISO designed siliconised plungers (left) versus OmniflexCP® (right) as determined by Finite Element Analysis (FEA).

and blue curves in Figure 5 it is clear that plunger siliconisation plays a critical role in stick-slip behaviour. Silicone oil distribution, in the region where the plunger and barrel are in contact, has the potential to be non-uniform and change with plunger placement method and storage. For example, when a siliconised elastomeric plunger is compressed in contact with a siliconised syringe barrel, the liquid silicone oil can be squeezed out from between the plunger and barrel.[10] This could result in areas of less lubrication on the barrel at the plunger rill / barrel contact points and areas of more lubrication between the plunger rills where the migrating silicone oil has settled. Thus, as it begins to traverse the length of the barrel, the plunger can stick and then slip and has the potential to undergo dynamic axial deformation. This in turn leads to glide forces that can oscillate between high and low. Figure 7 depicts this situation for a traditional siliconised plunger.

The two images at the top in Figure 7 show two positions of the plunger in contact with the barrel (grey bar) – first in the storage position (a) and then after all sealing surfaces have completely passed the initial storage position during injection process (b). The darker grey area on the barrel indicates where there is the high potential for non-uniform silicone oil distribution due to migration during plunger placement and/or storage. This region, from the leading rill to the trim edge, has a total length of approximately 6.8 mm as estimated from FEA simulations. This length reasonably correlates to the distance between the first and last peak maxima of the red curves in Figures 5 and 7 (siliconised plungers), which was determined to be 6.6 ± 0.2 mm for 10 curves selected at random. Figure 7a corresponds to the first peak maximum in the graph below, when the plunger movement is first initiated. By the time the plunger has completely passed the initial storage position, as in Figure 7b, the oscillating forces have largely been damped, which would correspond to the displacement beyond the last peak maximum.

Since OmniflexCP® is not siliconised, there is no opportunity for liquid silicone oil from the plunger to be redistributed during plunger placement or during storage. The baked-on silicone of the syriQ® InJentle syringe and the fixed, lubricious OmniflexCP® coating, together result in a significant reduction in stick-slip behaviour and overall, highly consistent delivery forces.

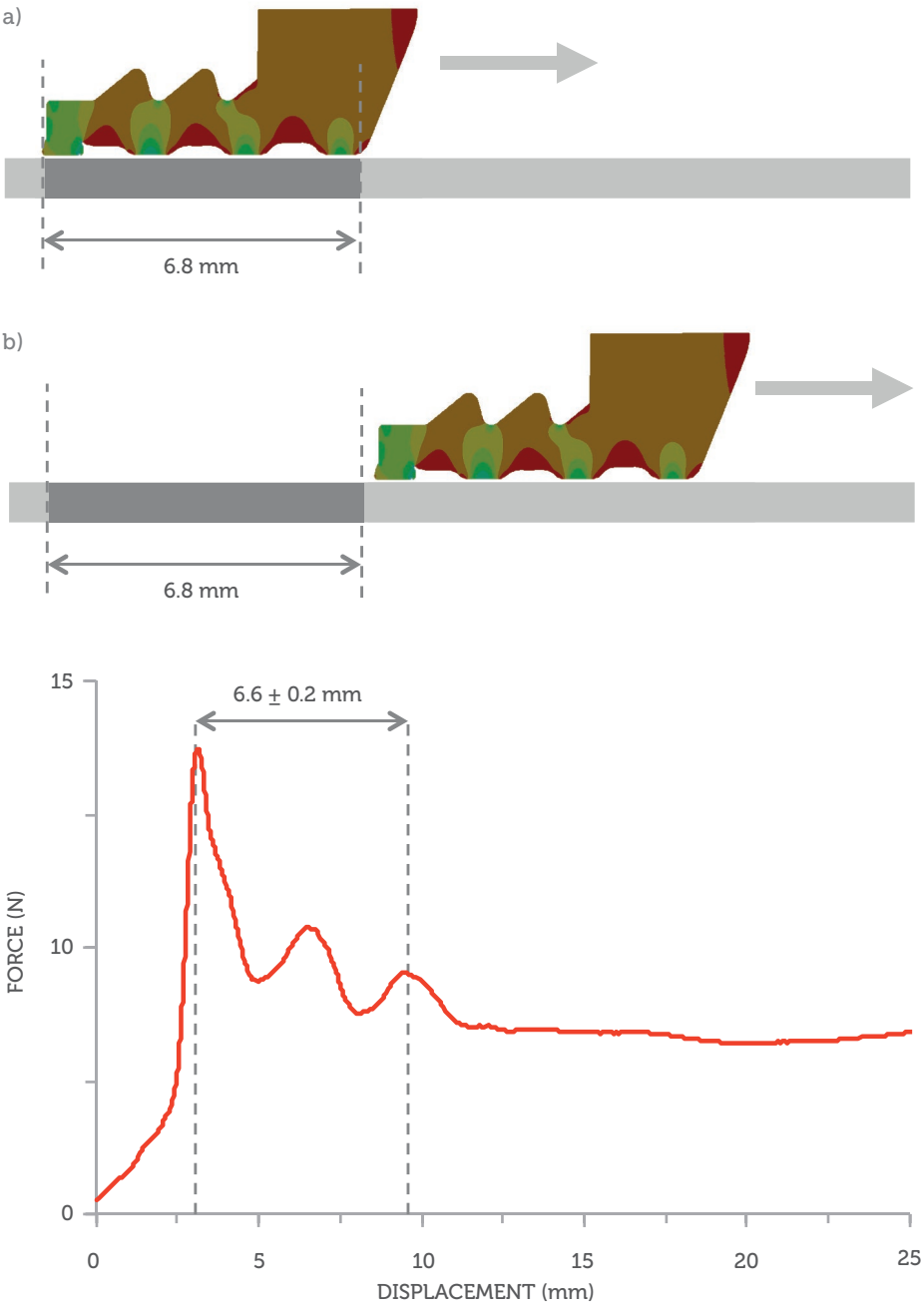


Figure 7: Stick-slip behaviour of siliconised plungers. The two images at the top show plunger in storage position (a) and then after all sealing surfaces have completely passed the initial storage position during injection process (b). Darker grey area on the barrel indicates where there is the high potential for non-uniform silicone oil distribution due to migration during plunger placement and/or storage. Graph below shows typical delivery force profile for a siliconised plunger experiencing a stick-slip behaviour. Average distance between the first and last peak maxima in the graph has a reasonable correlation to the length of the plunger/barrel contact zone.

SUMMARY

The combination of OmniflexCP® and the syriQ® InJentle syringe provides an integral solution to the challenges associated with ophthalmic and other precision injection applications. Since OmniflexCP® is not siliconised and since the syriQ® InJentle syringe has many unique features and uses baked-on silicone technology, silicone oil levels are reduced over traditional prefilled syringe systems.

The reduction of silicone levels while maintaining syringe functionality is key to minimising complications after intravitreal injections and helps to ensure superior compatibility with biologic drugs during long-term storage. The OmniflexCP® plunger design and absence of migrating silicone oil enable highly consistent delivery forces without stick-slip behaviour. Smooth glide forces are critical for precision injection applications such as ocular drug delivery as well as for pump-delivery applications.

OmniflexCP® is the leading fluoropolymer barrier coated plunger to provide ultra-low SbVP levels, no siliconisation, highly consistent delivery forces, superior chemical compatibility, and design flexibility.

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Innovative Automated Inspection
of pre-filled syringes with AIM 8000 series

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Bosch offers complete lines for pre-filled syringes from a single source – from water treatment, filling, closing and inspection to assembly and labeling, as well as secondary packaging. As an essential part of these lines, Bosch provides innovative inspection technologies, which ensure final product quality and contribute to patient safety.

Long-term inspection experience

As a leading manufacturer of inspection machines, Bosch offers equipment for both liquid and solid dosage forms. The first automated inspection machine was developed by Eisai Machinery (now part of Bosch Packaging Technology) in 1975. Over the years, more than 1200 machines have been installed by Bosch in more than 50 countries and have set the standard for automated inspection.

Versatile AIM 8000 series

The AIM 8000 series is the highly versatile and flexible inspection platform, allowing rapid customization according to each customer's requirements:

- Up to 600 containers/min
- Wide diameter and container height ranges
- For syringes, cartridges, vials, ampoules

Inspection for particles

- **Camera-based technology** for particles in all liquids (with optimized performance for high viscosity media and suspensions)
- **Light transmission based SD (Static Division) technology** for particles in low to medium viscosity liquids and liquid fill levels

The characteristics of the products to be inspected and the inspection requirements determine the inspection methodology.

Inspection for cosmetic defects

- **Camera-based technology** for lyophilized products, cosmetic container defects and liquid fill levels

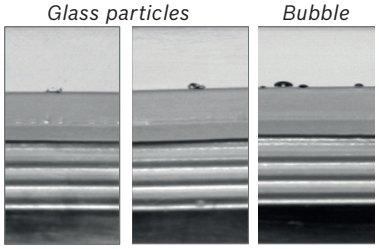
AIM 8000 series

Inspection for Container Closure Integrity (CCI)

- **CCI testing by high-voltage leak detection and headspace analysis**

Advanced inspection solutions

Pre-filled syringes pose special challenges to the inspection process. They must be inspected to detect floating and in-liquid particles, as well as particles on the stopper and siliconized walls. Moreover they require cosmetic inspection of a large number of items (for example luer lock, flange and needle).
The AIM 8000 series is especially suited for these complex inspection tasks. An example is the two-step approach to remove the influence of air bubbles on inspection results. First, the pre-spin system of the AIM 8000 helps to remove air bubbles from the liquid and the stopper. Second, a sophisticated imaging processing method is applied to distinguish particles from remaining air bubbles.
Each AIM 8000 is a complete system that ensures low false rejects and highest performance levels; with an approach that is easy to set-up and easy to validate.
Thanks to the optimal combination of the latest CMOS camera and SD technologies, as well as CCI testing modules, the AIM 8000 series offers a customizable high-end solution to meet the most challenging inspection requirements for pre-filled syringes.



Particles/Bubbles on stopper

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FLEXIBLE INSPECTION OF PREFILLED SYRINGES

With the advent of new and highly potent drugs, the market for prefilled syringes is growing continuously. These devices pose special challenges to the inspection process. They require both particle and cosmetic inspection for an increasingly large number of items. Here, Joachim Baczewski, President of Bosch Packaging Technology K.K. in Japan, and Global Responsible for Inspection Technology, describes how leading equipment manufacturers such as Bosch Packaging enable pharma companies to achieve target product quality with flexible processes, by offering a combination of innovative inspection systems for prefilled syringes and other containers

Due to an increase of chronic diseases such as diabetes and cancer, a rising number of patients require injectable drugs for self-administration. Prefilled syringes enable highly accurate dosing and decrease the exposure to potent products while, at the same time, they significantly reduce the danger of dosing errors and contribute to overall patient safety. As a result, the market for prefilled syringes is set for further growth. According to a recent market report,[1] worldwide production of prefilled syringes will almost double again by 2020.

TARGETING THE HIGHEST QUALITY STANDARDS

Since any container defect or change in the drugs' structure poses a serious threat to patient safety and product quality, both prefilled syringes and medicines necessitate thorough inspection. Subsequently, pharmaceutical manufacturers require sophisticated and versatile inspection technologies to meet the highest quality levels at all times. These technologies are used either for the detection of product-related contamination, container defects, leakages or all of them.

Product contamination implies the undesired introduction of impurities of a chemical or microbiological nature, or of foreign matter into or onto a raw material, intermediate, or API during production, sampling, packaging, storage or transport.[2] Cosmetic container defects, on the other hand, can occur during handling, either by human intervention or by incorrectly set-up machinery. Leakages of containers or closures might entail microbial ingress and reduced shelf life. To ensure that no contaminated products can enter the market and reach the patient, highly accurate inspection is required.

Inspection technologies range from manual and semi-automated through to fully automated, high-speed machines. When performing manual inspection, each syringe is inspected with fluorescent light against a black and white background. As manual systems remain subject to human errors and do not offer the speed required for larger batches, they are mainly used for customised applications and stability surveys. Semi-automated inspection systems can achieve more accuracy and reduce the need for manual handling. Automatic feeding, sorting and discharging functions enable inspectors to focus entirely on the quality control of prefilled syringes.

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AUTOMATED INSPECTION FOR FAST, HIGHLY ACCURATE RESULTS

Automated particle inspection systems have their origins in the 1970s. One of the original automated inspection principles is the Static Division (SD) system, which was developed by Eisai Machinery (now part of Bosch Packaging Technology). The SD (Figure 1) system derives its name from the ability to differentiate static from moving objects. It transmits light through the solution within the container onto an optical SD sensor. The prefilled syringe is rotated and then suddenly stopped and the liquid continues to rotate in the immobile container. Foreign particles moving inside the liquid block a portion of the transmitted light and cast a shadow, which is detected by the SD sensor.

Automated camera-based systems are used for both particle and cosmetic inspection and are either based on complementary metal oxide semiconductors (CMOS) or on charge coupled device (CCD) sensor technology, and are used in area or line scan cameras. Combined with specially designed optics and lighting such as LED (Figure 2), camera-based systems also ensure highly accurate inspection of product defects such as particles stuck to the sidewall, fill levels and product color, as well as container flaws such as cracks in syringe flanges. The latest CMOS-based systems even identify particles inside medium to highly viscous products, oils and suspensions. During rotation, the cameras take a sequence of images. These images are compared and analysed via sophisticated algorithms. The system identifies target defects while ensuring a low false reject rate. Product-specific parameters determine whether the syringe is rejected or accepted.

POWERFUL COMBINATIONS

The fully automated inspection series AIM 8000 (Figure 3) aims at high detection rates, even for suspensions and viscous products, and detects particles floating inside the liquid or sticking to the syringe's plunger stopper. A combination of transmitted and reflected light furthermore enables manufacturers to simultaneously detect light and dark colored particles on the same inspection station, thus leading to

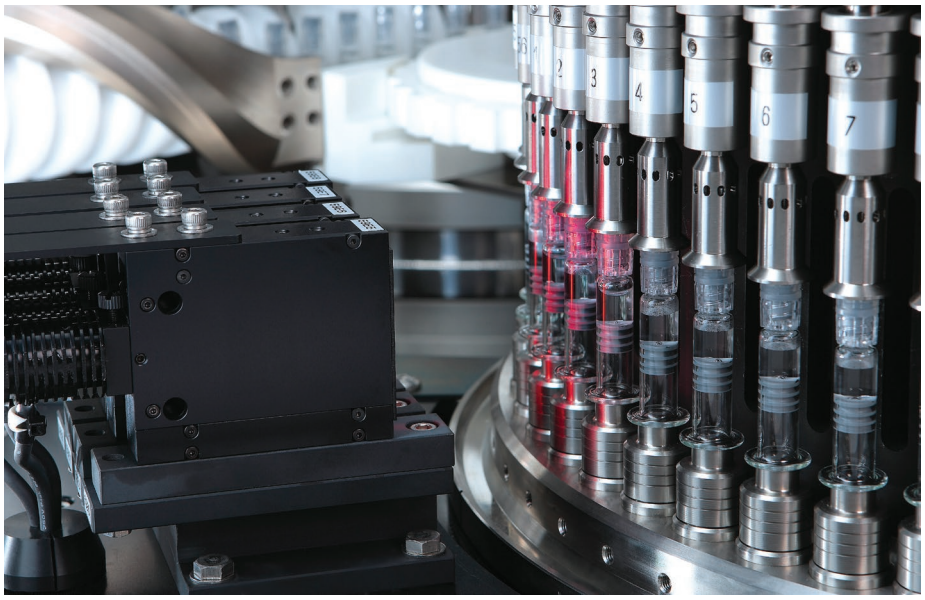

Figure 1: For 40 years, the SD technology keeps improving to meet the most challenging customers' requirements.

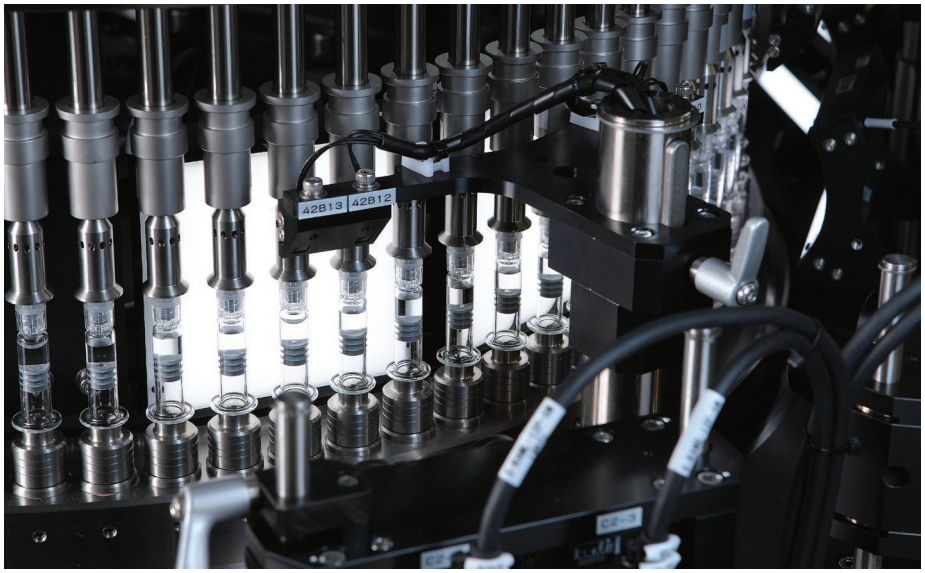

Figure 2: Inspection system with LED lighting.

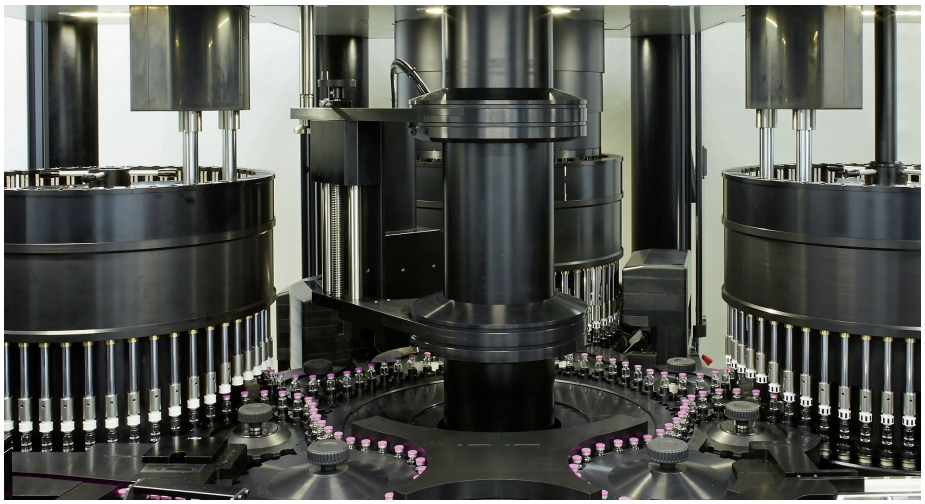

Figure 3: The AIM 8000 series is the most versatile inspection platform allowing rapid customisation to each customer's requirement.

significant space savings compared to the usage of two separate stations for each of the inspection methods. The latest pre-spin technology caters to the special inspection requirements of prefilled syringes by removing bubbles from the plunger stopper at elevated speeds. Moreover, the machine allows cosmetic inspection of a large number of syringe items, such as the needle shield, shoulder, or flange.

To meet the industry's rapidly changing requirements further, the AIM 8000 series offers a hybrid approach by integrating both SD and camera-based inspection technology in one flexible platform. This enables pharmaceutical manufacturers to adapt their inspection processes to their individual production and product needs beyond the conventional scope. Next to prefilled syringes, this equipment is also designed for the inspection of other containers such as vials, ampoules and cartridges, offering flexibility to manufacturers. The modular design facilitates the expansion of existing systems by integrating additional inspection units or adding an extra inspection module. In addition, Container Closure Integrity (CCI) testing via high-voltage leak detection or headspace analysis can be integrated into the AIM 8000 platform on request.

CCI has steadily moved up the agenda in recent years.[3] Studies show that prefilled syringes are also prone to CCI defects, which might be even more hazardous than particles when they lead to a change in the API. CCI methods allow pharmaceutical manufacturers to detect sterility breaches prior to product contamination, and prove to be less time-consuming than most commonly used sterility testing methods. State-of-the art inspection platforms are able to incorporate tailored CCI testing systems for prefilled syringes. For instance, high-voltage leak detection (HVLD) measures the electrical resistance of the syringes with conductive solutions. Headspace analysis (HSA) measures the quantity of light passing through the headspace region via laser spectroscopy, and is applicable to lyophilised products and medicines filled under vacuum or purged with gas. Vacuum leak detection (VLD), in turn, measures vacuum or pressure decay in a dedicated chamber.

CONSIDERATIONS FOR THE EFFECTIVE USE OF INSPECTION EQUIPMENT

Utilising state-of-the-art technologies starts by thoroughly testing the inspection methods with product samples before choosing the equipment. After the installation of the equipment, operator qualification and training, as well as regular maintenance of the equipment by competent service personnel, is required. Retrofitting additional inspection equipment and adapting it to new products and/or inspection requirements, as well as complete system modernisations should also be considered as key factors for the selection of the ideal inspection equipment.

> "CCI methods allow pharmaceutical manufacturers to detect sterility breaches prior to product contamination, and prove to be less time-consuming than most commonly used sterility testing methods"

The above is especially true for the inspection of prefilled syringes with their various inspection criteria and steps. Assuring the highest quality and lowest false-reject rates throughout the lifespan of this machinery will not only bring quality benefits to patients but also economical benefits to pharmaceutical producers.

Paying close attention to the requirements for prefilled syringes, Bosch offers an extensive portfolio of dedicated inspection equipment ranging from manual to fully automated high-speed systems. A special focus is set on the combination of different technologies for particle and cosmetic inspection, as well as CCI. As a competent partner to the industry, Bosch also supports pharmaceutical producers in improving their entire production process, for instance by integrating inspection equipment into complex production and packaging lines. Highly qualified scientists and engineers at Bosch ensure that Bosch is the ideal partner for all inspection requirements, including the rapidly expanding market for prefilled syringes.

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ABOUT BOSCH PACKAGING TECHNOLOGY – PRODUCT DIVISION PHARMA

Bosch Packaging Technology – Product Division Pharma is one of the leading providers of process technology and packaging solutions for the pharmaceutical industry. The portfolio includes single units, complete lines and integrated systems for the manufacturing and processing of liquid and solid pharmaceuticals. It also includes process technology, primary packaging, inspection technology for different application fields and packaging types. Secondary packaging with qualification and validation, software solutions for track and trace and technical customer service are also available.

The following product brands are part of the Bosch portfolio for the pharmaceutical industry: Hüttlin, Klenzaids, Manesty, Moeller&Devicon, Pharmatec, SBM Schoeller-Bleckmann Medizintechnik, Sigpack and Valicare. For more information, please visit www.boschpackaging.com.

ABOUT BOSCH PACKAGING TECHNOLOGY

Based in Waiblingen near Stuttgart, Germany, and employing 6,100 associates, the Bosch Packaging Technology division is one of the leading suppliers of process and packaging technology. At over 30 locations in more than 15 countries worldwide, a highly-qualified workforce develops and produces complete solutions for the pharmaceuticals, food, and confectionery industries. These solutions are complemented by a comprehensive after-sales service portfolio. A global service and sales network provides customers with local points of contact.

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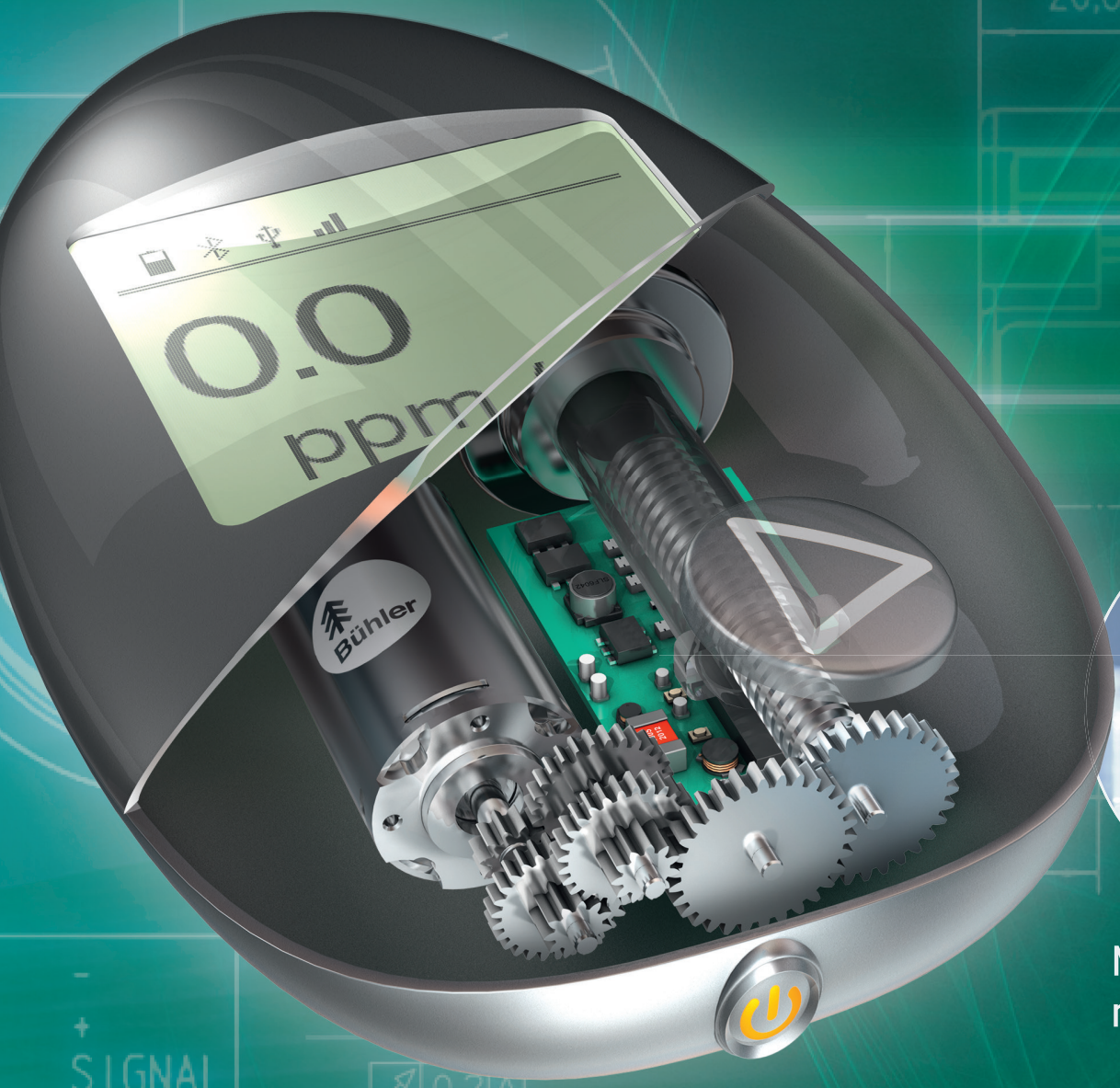

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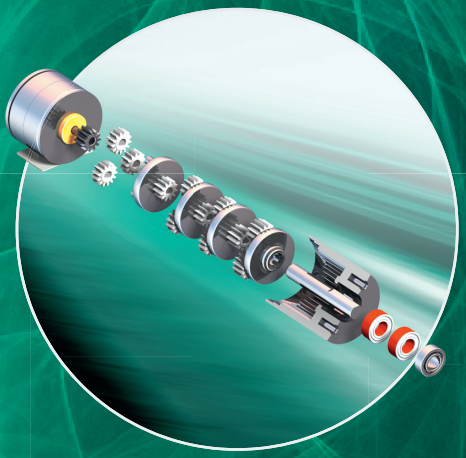

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STEAM STERILISATION: A NEW OPTION FOR OMPI EZ-FILL VIALS & CARTRIDGES

Pharmaceutical primary packaging for parenteral drugs is increasingly commonly provided in pre-sterilised nest and tub configuration. Nowadays, sterilisation – one of the most critical parts in the production of ready-to-fill glass containers – is applied by their manufacturers mainly through ethylene oxide (EtO). This method has served the market well for many years, but as drugs and delivery devices have advanced, some limitations have become apparent. The rapid rise in biological drug development is expanding the market for new sterilisation technologies that can overcome the limitations of current method and facilitate innovation and progress in the pharmaceutical and biotechnology industries. In this article, Andrea Zambon, Product Manager, EZ-fill Vials & Cartridges at Ompi Pharmaceutical Systems, explains how, in compliance with the European and United States Pharmacopoeias, the company is therefore now offering a totally new option for ready-to-fill glass containers: steam sterilisation for vials and cartridges.

Sterilisation of pharmaceutical primary packaging for parenteral drugs has always been a sensitive topic for pharmaceutical companies. Since the introduction of the first ready-to-fill containers (syringes) in the market during the 1970s, national regulatory bodies have always had a special consideration for this specific phase of the process, in order to guarantee the safety and the health of patients.

The sterilisation method used during the process depends primarily on the nature of containers, closures and packaging material.

> "The percentage sales from biotechnology products (bioengineered vaccines & biologics), within the world's top 100, is set to increase to 46% in 2020, whereas in 2006 it was 21%.8"

Ethylene oxide (EtO) sterilisation is largely used in the market by ready-to-fill glass containers producers and it became a standard for most of their sterilisation processes.

EtO is basically a gas that operates through alkylation of sulphydryl, amino, carboxylic, phenolic, hydroxyl, phenolic group of structural proteins and enzymes. Its typical treatment conditions are generally characterised by:

- gas concentration between 200 and 1000 mg/L
- temperature 30°C for cold cycle and 60°C for warm cycle
- time between 1.5 and 12 hours
- variable pressure depending on the EtO presence (usually it could be blended with other substances such as nitrogen or carbon dioxide).

Sterilisation method for pharmaceutical primary containers is a highly regulated topic. Even though EtO sterilisation is largely validated and used in the market, according to US/EU Pharmacopeia and GMP guidelines it should only be used when no other method is practicable. This is in order to ensure that any residue of gas or its degradation products in the sterilised product is below the concentration that could give rise to toxic effects during the use of the product. To avoid any doubt about it, during process validation it is always required to show that there is no damaging effect on the product. For example, the parameters and limits of the EtO

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sterilisation cycle (e.g. temperature, pressure, humidity, gas concentration, exposure time, degassing, aeration time and determination of residuals) should be specified and monitored closely. At the same time, the need to monitor the EtO sterilisation process rigidly makes this option more comprehensive than others.

For all these particular reasons, selecting the appropriate process for a given dosage form or component requires a strong knowledge of sterilisation techniques and information concerning any effects on the material that will be sterilised.

EtO sterilisation is frequently selected when the material to be sterilised cannot withstand the high temperatures obtained during steam sterilisation.[1-7]

Besides all the important regulatory aspects, the need for an alternative sterilisation method in addition to EtO is all the more necessary if we look at the rapid rise in biological drug development, where a lot of unstable molecules that can react with the primary containers are under development.

Most of the new drug products being developed today are biologics, such as therapeutic proteins. The percentage sales from biotechnology products (bioengineered vaccines & biologics), within the world's top 100, is set to increase to 46% in 2020, whereas in 2006 it was 21%.[8] Having a new way of approaching drug/container interaction especially for biotech drugs is now a "must have" and not a "nice to have".

Candidates include injectable solutions, peptides and vaccines. Residual agents such as EtO in fact can yield adduct formation for low-dose protein therapeutics. Due to its structure, EtO is counted among the very reactive compounds. The reactivity includes with organic structures within cells and cell nuclei (DNA, RNA and proteins).[9] Formulation development teams in fact should be considering evaluating possible effects of product exposure to trace quantities of EtO.[10]

In order to answer this new and complex scenario, Ompi Pharmaceutical Systems started to develop its specific solution based on steam sterilisation. This process led Ompi, back in 2012, to add first steam sterilised barrels and then pre-capped steam-sterilised cartridges into the portfolio. Nowadays, as part of that continuous desire to enlarge the product offering, the portfolio is about to list brand new Ompi EZ-fill Vials sterilised through steam sterilisation (Figure 1).

Before going into the detail of the Ompi EZ-fill steam sterilisation solution it is useful to provide an overview of the entire

Figure 1: Ompi EZ-fill Vials in nest & tub.

Ompi EZ-fill Vials & Cartridges process. It is described as follows:

- **incoming materials:** all the raw materials for Ompi EZ-fill Vials & Cartridges undergo incoming inspections that are necessary to declare them suitable for ISO7 / ISO5 production. Vials and cartridges are supplied to the Ompi EZ-fill area (ISO8)
- **washing:** vials and cartridges are washed into the validated washing machine by WFI (Water For Injection)
- **siliconisation:** cartridges can be optionally siliconised (baked silicone)
- **heating:** drying and depyrogenation is performed through an oven. Cycle is optimised for each format in order to reduce the exposure time and assure optimal drying
- **capping:** cartridges can optionally (upon customers' requests) be pre-capped with selected rubber formulations
- **packaging:** vials and cartridges enter the ISO7 and ISO5 area and are placed into two main packaging configurations:

1) **Tray:** box made out of a single injection mould preventing glass-to-glass contact between containers during transportation and storage

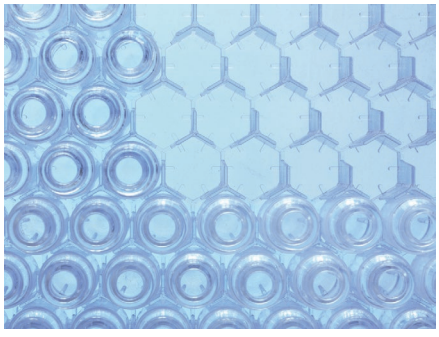

Figure 2: No glass-to-glass contact in Ompi EZ-fill tray packaging.

2) **Nest & Tub:** standard nest & tub configuration as the PFS solution one, preventing glass-to-glass contact (Figure 2).

Both configurations are sealed by a Tyvek® lid and packaged in single or double steribags. Final pallet configuration takes place according to the procedure determined by the specific sterilisation media desired. Key attention is given to the cleanliness of the packaging components as to the production of the glass container itself

- **final sterilisation:** according to desired sterilisation media.

Generally speaking, with steam sterilisation, saturated water vapour is blown inside a dedicated autoclave. This is properly equipped with an external jacket aimed to stabilise the conditions of temperature and pressure inside it across the entire sterilisation cycle.

Steam sterilisation at Ompi Pharmaceutical Systems today is actually performed by a highly specific and well-designed cycle that is the result of a long study on all its critical parameters and their interconnections. The main critical parameters are:

- Temperature
- Pressure
- Time
- Packaging materials & their configuration.

What is interesting, and what Ompi is particularly proud of, is that all these parameters are not simply held constant throughout the entire cycle but they are made to vary in highly specific way in order to get the best result in terms of the quality of the sterilised final product.

Another key point of the whole Ompi steam sterilisation project is that glass pharmaceutical containers intended for steam sterilisation are treated using the same process, honed over 40 years, as the ones

Figure 3: The autoclave used in steam sterilisation is equipped with an external jacket aimed to stabilise the conditions of temperature and pressure inside it across the entire sterilisation cycle. Saturated water vapour is blown inside.

intended for EtO sterilisation. Moreover, this also means that Ompi developed its steam-sterilised solution without changing final packaging configuration from the EtO-sterilised configuration.

In fact, as mentioned above, during the Ompi EZ-fill process, glass pharmaceutical containers are washed, depyrogenised, packed inside Nest & Tub or Tray configuration, bagged in single or double steribags and finally packed in regular Ompi EZ-fill boxes, either in case of EtO sterilisation or in case of Steam sterilisation (see Figure 4).

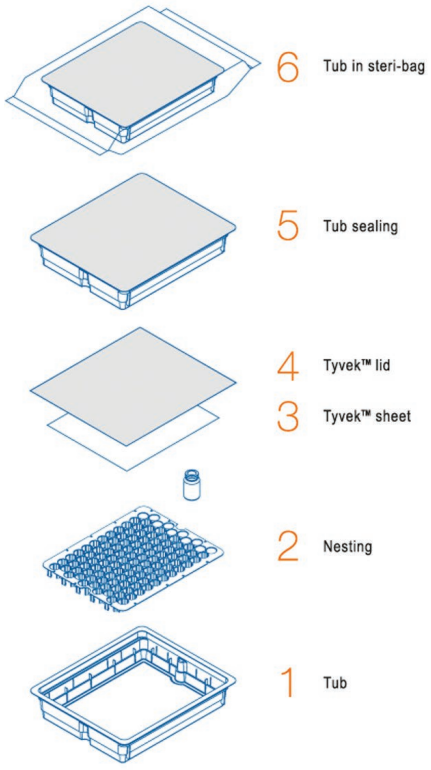

Figure 4: Ompi EZ-fill Vials in nest & tub: configuration explosion.

EtO sterilisation has always been performed outside Ompi facilities by qualified sterilisers. In contrast, steam sterilisation is run internally by means of a dedicated proprietary Ompi autoclave. This said, steam sterilisation is not performed on a full pallet but on bagged nest & tub or tray units. Pallets addressed to customers are then built up after the sterilisation phase.

Ompi meticulously designs packaging configuration and composition together with its specialised suppliers. This is an important phase of the process because these elements have to allow water vapour to reach the inside surfaces of glass containers and sterilise them. In the same time, they are a critical barrier that guarantees sterility across transportation of the final product and storage at the customer.

CONCLUSIONS

Even if EtO is the most commonly adopted sterilisation method in the market by ready-to-fill container producers, an alternative to this type of sterilisation is demanded both by regulation authorities, and drug development trends point only to this demand increasingly strongly. Following these requirements, Ompi developed its own steam sterilisation for cartridges, now extended to vials (Ompi EZ-fill Vials) in order to be even closer to authorities and customers' needs, giving an important alternative for this crucial phase in the production of ready-to-fill glass containers without changing the final packaging configuration.

Beginning October 2015, Ompi is introducing the first validated formats of Ompi EZ-fill Vials with steam sterilisation (from 2R to 8R) that are going to be added to the pre-capped cartridges already offered on the market with this kind of sterilisation. Its aim is to widen its steam-sterilised portfolio in the coming months.

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PRODUCT PROFILE: **PREMIUMCOAT™**

Aptar Stelmi

PREMIUMCOAT™ COATED STOPPERS FOR SENSITIVE HIGH-VALUE INJECTABLES

Earlier in 2015, Aptar Stelmi, the industry's trusted global partner, providing premium elastomeric closure systems for injectables, announced a new addition to its broad portfolio of products with the introduction of a novel range of coated stoppers called PremiumCoat™ (Figure 1), designed for the protection of sensitive and high-value drugs, including biopharmaceuticals.

Figure 1: PremiumCoat™ stoppers are designed for the protection of sensitive and high-value drugs, including biopharmaceuticals. (Image courtesy of Aptar Stelmi).

SENSITIVE, HIGH-VALUE INJECTABLES, A DYNAMIC MARKET

Sensitive and high-value injectables encompass complex and potent drugs manufactured by chemical synthesis, and biological agents engineered in a living system such as a micro-organism, plant or animal cell. They include cytotoxic drugs used in cancer therapies, novel vaccines, blood derivatives, hormones and many compounds used to treat auto-immune diseases, including monoclonal antibodies.

The market for biologics represents 20% of the global drug market with growth at a CAGR of 10% in 2010-2015, twice that of the global drug market.

SENSITIVE AND HIGH-VALUE INJECTABLES REQUIRE PREMIUM COMPONENTS

Sensitive and high-value injectables are fragile by nature. Therefore, maintaining the integrity of the container closure while minimising interactions between the drug compound(s) and the component constituents is a challenge. Conventional elastomeric closure systems may not be an optimal solution for these fragile drugs.

PremiumCoat™ is a novel range of elastomeric stoppers developed by Aptar Stelmi. The surface of the elastomer is coated during manufacturing with a thin fluoropolymer film. This coating acts as an effective barrier to many of the extractables and leachables that can be released from the elastomer and contaminate the drug. As a result, compatibility of the drug and the closure is significantly superior with PremiumCoat™ stoppers.

"The past three years we have spent developing the technology and then preparing for this new product launch have been very exciting. PremiumCoat™ is the first product in our range of innovative solutions for high-value injectable drugs," said Ghislain Fournier, Industrial & Technical Director, Aptar Stelmi, at the time of launch.

ABOUT APTAR STELMI

Part of the Pharma division of AptarGroup, Inc, Aptar Stelmi is a trusted partner of leading pharmaceutical companies in the design and manufacturing of elastomeric closures for parenteral applications. Driven by quality, service, and innovation for more than 50 years, Aptar Stelmi products meet the evolving drug industry demands for cleanliness, efficiency and compliance. Our prefilled syringe components and stoppers for vials are used to multiple applications in more than 70 countries worldwide.

AptarGroup, Inc (NYSE: ATR) is a leading global supplier of a broad range of innovative dispensing systems for the beauty, personal care, home care, prescription drug, consumer health care, injectables, food and beverage markets. AptarGroup is headquartered in Crystal Lake, IL, US, with manufacturing facilities in North America, Europe, Asia and Latin America.

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INTERVIEW: JOHN A. MERHIGE, CREDENCE MEDSYSTEMS

Credence MedSystems is an award-winning medical device company based in Menlo Park, California, in the heart of Silicon Valley, developing a platform of innovative, fully passive injection safety devices that fully serve both needlestick prevention and auto-disabling functions without impacting on the drug product manufacturing supply chain.

The Companion System was first introduced by Credence's Chief Commercial Officer, John A. Merhige, in previous feature articles in ONdrugDelivery Magazine (September 2014, Issue 52, pp 10-12, and February 2015, Issue 55, pp 45-46). We were pleased to have the opportunity to speak with him live recently, and dig a little deeper into the company's history, the people behind it, and the devices it is developing, and to discover not only more about what the company's core philosophy, "Innovation Without Change" is really about, but how much it genuinely means to Credence.

Q Many readers of ONdrugDelivery Magazine will already be familiar with Credence MedSystems, but perhaps you could start by giving us an overview of the company's main product offering, the Companion Safety Syringe System, the main elements it comprises, and what the system does?

A At its core the Companion is a product family of advanced syringe delivery systems, and they all have critical safety features and critical usability features for the end user. In that family we've got a staked-needle solution, a luer lock solution, and we now have a dual chamber reconstitution safety device as well. The family has expanded in a very short time but all of the devices share that same safety feature of offering passive needle-stick safety.

The user performs the injection, they complete the injection and receive cues that the dose is complete. Many folks talk about "safety activation cues" but in this system they are end-of-dose cues. It's an important distinction. So they receive the cues and then automatically and passively the needle retracts into the barrel of the syringe where it is safely contained and the syringe is permanently disabled from future use.

Really that's one of the things that led to the choice of the name "Companion"; that fundamentally these devices help protect the user, be they a nurse or a self-injecting patient, just like a trusted friend or companion can do. So fundamentally these are passive safety devices. But that's only half the story of the system though. There's more – which we can talk about later.

Q The injection safety device space is extremely crowded and highly competitive. Credence says it offers *Innovation Without Change* as a differentiating factor. Could you describe how the concept of *Innovation Without Change* is more than just a marketing line? How does it relate back to the technical design and form of the Companion Safety Syringe System and, crucially, how does it translate into a real-world advantage for your pharma partners?

A Well, this is indeed a crowded space, and sometimes I think the technology that is out there isn't really where it should be. But then I realise that we have really only been talking about these devices for 15 years or so, when things really started moving along with the Needlestick Prevention Act in 2000. Compared with how long needles and syringes have been around these are relatively new and so it's fair that the technology is still evolving.

> "While this company is still fairly young, the team is not!! We've all been around a long time and we've been very fortunate – each of us – to have brought multiple companies from technology invention to product development and through to commercial launch and scaled manufacturing volumes."

Getting back to your question, *Innovation Without Change* is so much more than a tag line. It's truly Credence's core philosophy. It's our corporate philosophy. It's our design philosophy. It's our business partnering philosophy. It really has permeated everything we do because, from our perspective, it is so obviously the right approach.

So let me explain where it comes from and what it's all about. Well it has come from a simple idea. In this space, everything we do – from manufacturing to design to corporate partnering – should be done with both the end user performing the injection in mind *and* the drug company in mind. Our partners and the end users need to *always* be omnipresent in the decision making process.

More tangibly, if we take this down from the philosophical to the more practical, *Innovation Without Change* means this: we offer the *Innovation* of the final device that is placed in the end-user's hands, with all of its safety and usability features, *Without the Change* that typically comes along when drug manufacturers perform drug device combination development.

So, how do you achieve this idea of *Innovation Without Change*? I think the easiest way to think about it is that the Companion System uses a modular approach. Drug manufacturers are able to select any primary package component they want out of all and any that exist today, from the syringe barrel (which can be from any manufacturer, any size, made from glass or plastic) to the stoppers (for example standard butyl or Fluorotec coated for sensitive biologics), to the tip-caps, and the needleshields. These can all be sourced from any combination of vendors the drug companies choose. The point is that the Companion works around those choices.

The Companion needle is either pre-attached if the product uses a staked-in syringe, or is attached by the user if it's a luer. And the Companion plunger rod is assembled in secondary packaging just the way plunger rods are assembled today. So we build everything around the core choices of primary package components that work for the drug manufacturer, for the specific drug and the specific user population.

As an aside, that's the other side of where

the Companion name comes from. The Companion components *accompany* the existing primary packaging. And for that reason the choice of name Companion was an obvious choice for us and it has resonated with our partners and our customers.

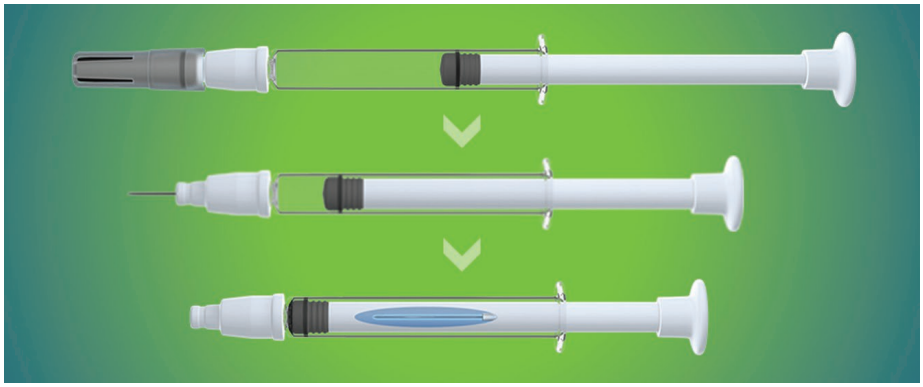
Innovation Without Change, keeping those existing components, not having to change them, is massively important. There is data in the literature that quantifies the consequences of changing primary packaging components and it's somewhere around three years and several million dollars of development. Our approach simplifies that process. We let the manufacturer choose their component, we simplify the development process and the commercialisation process and, just as importantly, we fit into the existing supply chain seamlessly.

This allows us and our pharma partners to leverage the expertise of their trusted vendors who have been perfecting their craft of making syringe and closure components for a long, long time. Alternative solutions in the market seem to hold the drug manufacturer captive to a single source supplier. That's absolutely not our approach. Instead we give the manufacturers the ability to dual source their syringes and other critical components and we take out the risk that could come from disrupting the supply chain.

The other thing I really think is worth looking at is not just the design and development side but the impact – or lack thereof – to the manufacturing environment. We all know that change is really hard in this drug development world. It should be of course, but the fact that change is so hard has left good technologies on the cutting room floor, because they were too costly or too risky to implement.

So what's the Companion's impact on the manufacturing environment? First of all, aseptic fill-finish is completely unchanged. The filler – whether it be the drug manufacturer or a contract filler – will receive the syringes in the same conventional tubs that they are used to receiving them in. The syringes are compatible with ready to fill or bulk lines. So filling is unchanged.

Just as importantly, the impact of secondary assembly is really significantly minimised. All we've got to do is assemble the plunger rod. The finger flange is optional – the manufacturer can opt to have it or not, and that decision is driven by human factors studies in a particular application. But essentially all they have to do is screw in a plunger rod, just as they are conventionally doing today, and we're done. The system is put together. In contrast, the most prevalent of needlestick safety devices have significant secondary assembly steps to wrap the exoskeleton cage around the syringe. That drives a big capital investment, it drives the need for time, space on the floor, through to the cost of assembly.



The Companion Safety System provides passive needle retraction directly from the injection site with end-of-dose cues, is automatically and permanently disabled after injection, all without disrupting the existing manufacturing supply chain.

What we've done is make it easier for drug companies to do the right thing. They no longer have to sacrifice safety and usability in order to give their customers the right product, in order to give their marketers the differentiated product, in order to satisfy risk management and compliance.

So whilst *Innovation Without Change* is so much more and runs so much deeper than just being a tag line, nonetheless it is also a great tag line!

"Innovation Without Change is so much more than a tag line. It's truly Credence's core philosophy. It's our corporate philosophy. It's our design philosophy. It's our business partnering philosophy. It really has permeated everything we do because, from our perspective, it is so obviously the right approach"

Q The Companion received the "Award for Best and Most Innovative Advancement in Drug Delivery" at Drug Delivery Partnerships 2015 in Boca Raton, FL, US, and Credence MedSystems was awarded the "Innovation First Prize" at Pharmapack Europe 2015 in Paris, France, for its novel drug delivery system. But behind the award-winning products Credence is developing, there is of course a company, people and investors. Could you tell us a little about this aspect of Credence MedSystems? What is the company's history, the story of its founding, its sources of funding, and who are the key people who set-up and who run Credence MedSystems?

A It's kind of you to mention those awards, and for a younger company as we are, external validation is really important. We all work tirelessly because we think we do have that solution to address a global healthcare problem, in a way that benefits drug manufacturers and the end users. That external validation is so important because it tells us that yes, we are on to something. And those awards and frankly the progress we've made with lining up collaborations with drug companies, really are important in enforcing that.

To be honoured with major awards is just fantastic!

In a young company, the culture is so critical. In huge companies there are buffers. In a young company the drive that comes from knowing that we are doing something that is important, and having others tell us that, really does help people get out of bed in the morning.

The company was founded about two or three years ago in an incubator in Northern California called Reprise Medical. The incu-

bator was started by Credence's Chairman, Dr Frank Litvack and our Chief Executive Officer Jeff Shanley. So Frank and Jeff are extremely accomplished and have had a lot of success in medical technology. Frank is an interventional cardiologist turned successful entrepreneur. Jeff is a successful executive but he's also a first rate inventor and patent strategist. That's obviously very important for our company, which has a partnering model, to be secure in our own IP but also to give security to our collaborator that they are free to market. So it's extremely important.

Once they realised that this technology was deserving of its own company, they brought me and my partner, Jeff Tillack in, as well as the rest of our fantastic team. Jeff runs the operations, QA and development, whilst my focus is more external – partners, investors, marketing and sales and so on. So while this company is still fairly young, the team is not!! We've all been around a long time and we've been very fortunate – each of us – to have brought multiple companies from technology invention to product development and through to commercial launch and scaled manufacturing volumes. We've all had companies that have gone through successful public offering events or acquisitions or the like, so we've done this before.

Getting back to the company, we're based in the Bay Area of Northern California, right in the heart of Silicon Valley. As everybody knows, that area is absolutely ripe with technology and there is the air of inevitable success. Certainly every company doesn't succeed, but so many have in such a public fashion that it's an exciting culture.

Q We touched on differentiation earlier in terms of *Innovation Without Change*. What other ways does the Credence Companion Safety Syringe System stand out as offering something over-and-above the many other injection safety systems out there? And I'm thinking not only from the point of view of pharma/biotech industry partners but also about what this syringe safety system brings to the table for hospitals, healthcare professionals, patients and carers.

A Well this is really an important question and it takes us squarely back to *Innovation Without Change*, and keeping the drug manufacturer and the end user permanently in mind.

The user discussion has to start with passive needlestick safety. We just did another human factors study. This one was with a nursing population. Nine out of ten of them – 90% – had experienced a needlestick! This is just astounding. It simply has got to start with safety.

The legislation out there is directed towards healthcare providers in the formal healthcare setting. It's not yet directed towards home users or self-injectors. I think the first line of thought there was that they are injecting themselves so they are not going to get sick from a needlestick from their own needle. But you have to ask, what happens to the needle immediately after an injection? Does the grandchild or child or a sanitation worker or the housekeeper stick themselves? It's a population that has been left behind a bit and it shouldn't be.

> "I think the easiest way to think about it is that the Companion System uses a modular approach. Drug manufacturers are able to select any primary package component they want... These can all be sourced from any combination of any vendors. The point is that the Companion works around those choices... What we have done is make it easier for drug companies to do the right thing."

Just to review, with the Companion, the user simply performs the injection, gets the cues that the dose has finished and the needle automatically retracts to safety within the barrel of the syringe. The syringe is then disabled and cannot be used again. So we don't only think about needle safety during the initial injection but also about preventing re-use.

This is all at the heart of passive safety because we know that active approaches – that require specific action by the user – are ineffective. There is plenty of data to support that. One study in Massachusetts found that 75% of injuries occur from devices that already have safety features on board, the old style of approaches. Again, related to that whole experience are the cues – not just of safety activation but end-of-dose cues. So a nurse in a busy environment can simply inject with Companion until they feel the click and they know then that the entire dose has been delivered and that the needle is safe. It's a very important feature.

Beyond that, another aspect of Companion's design is allowing the syringe to be used the way people have been using syringes for hundreds of years. It allows the use to have full visibility of the syringe barrel and of the drug inside, which is critical for pre-injection inspection. The main products out there today do not allow that. The Companion allows the user to perform conventional operations like purging an air bubble, or aspiration to make sure they are not in a blood vessel. Whereas most other approaches out there specifically instruct the user not to do that because of the risk of premature activation of the safety feature. We like to say that Companion acts like a normal syringe when you want it to, but brings with it all of the other important features.

Finally, there's the design. One of the really revealing insights that has come out of our human factors studies over the years is that the user wants to trust the device. I don't want to be too grandiose about it but it's really an emotional trust they are looking for. The user experiences the device and measures that trustworthiness certainly by a history of reliable experience to some extent but also, more personally and maybe more palpably by the look and feel of the device in their hand. And so you do have to pay attention to the thumb pad, the finger flange, the overall fit. The product is designed to fit in the user's hand and look familiar so that the user can begin building trust. That ultimate trust comes down to, "Does that device protect me".

We were thrilled to see in our recent study that 100% of the users said that the device would protect them from needle sticks. It comes back to the name – we trust our companions. It's an important thing.

One more thing comes to mind - it's a bit more technical. The Companion is glue free. In existing staked syringes, it's adhesive which holds the needle in place. The fact that the Companion is glue free eliminates any risk of unwanted interaction or leaching between the glue and the drug product. It also enables certain lubrication techniques that reduce the level of silicone laid down which also reduces the risk of unwanted aggregation in sensitive drugs. Eliminating glue makes the product safer, lower risk, for everyone.

Q Let's say I'm a company interested in doing business with Credence. What kind of company is Credence to work with, in the context of a long-term partnership? What's its culture, and what are its driving forces and corporate philosophies? And also, day-to-day on the ground, what can I expect from a relationship with Credence MedSystems?

A We are a partnering company. Not just with our drug manufacturer partners, which is obvious, but with syringe manufacturers, with contract fillers, with the component suppliers. One of our customers said to us recently that this product should become ubiquitous. What he is getting at there is that because you are combining the added value of the device with the simplified de-risked approach to the drug companies, and the supply chain, it should become an obvious choice.

So we focus then on the supply chain. Once again, this brings me back to *Innovation Without Change* because Credence is evolving into a major presence in the supply chain. But we are doing this by playing nicely with others. There is every reason to assimilate in the supply chain and partner with these extremely successful supply chain partners that have been doing what they've been doing for a long time.

As for day-to-day, I love working with this company! I have worked everywhere from enormous manufacturing in the motor industry, to Credence where we started with one or two people. It is a place where people do what they do because they like doing what they do. You never have to worry about whether something is going to get done, or whether someone is going to go the extra mile. These are experienced people who have done it before and know what it takes and have taken the conscious decision to be at Credence because it is the right thing in their lives.

Beyond that I would say this – and I get to say this because while I was schooled as an engineer I have since moved on to a different functional focus – this is easily the best engineering team I've ever worked with. They *get* customer wants and needs, they bring invention into development quickly, the answer is never "no" and inevitably they come back with a solution to a problem. It's really just a pleasure.

Q The past year or so have been very successful for Credence, the industry has been introduced to the Companion System, and had a great reception, winning several awards and attracting the attention of serious players in the industry. What are the next steps? For the safety syringe system in particular, but also more broadly for the company and its medium/long-term strategy?

A I have to fight the temptation to be overly nostalgic or romantic but I really do think of it as a story that has chapters. Chapter one was focused on invention and intellectual property and development. That was when we were very internally focused, trying to work out how we could solve the problems of current approaches that we saw in the market.

Chapter two was a bit of a coming out party where we stepped into the industry's view, and that's always interesting. I remember we had a team meeting right before we went out and started showing the device and we thought, who knows what the reception is going to be? And I guess this is what makes this exciting and why we do what we do. Looking back on that chapter I don't think it could have possibly gone any better. We won the awards, and more importantly we've aligned with numerous customers who are at various stages of development and evaluation and implementation.

So looking ahead, chapter three has got to be about evolution. It's got to be about continuing to execute, and about scaling the manufacturing to meet the demand that comes as these devices progress through the development path with the pharma partners. You start with a couple of hundred of devices for evaluation and then a couple of thousand for human factors studies, and stability and so on. It's about evolving and growing while continuing to hammer the execution. And then of course it's about continuing to line up the pharma and biotech manufacturers as partners.

Success always begets success right! We're not a company that makes a lot of public announcements and we don't need to because of the way we're capitalised, but we're quietly lining up a lot of partners. With each one, the next one becomes a lot easier because we are a known entity, because we are continuing to grow our credibility in the industry.

It brings us back to the name discussion. There's a reason why the Companion is called the Companion, there's a reason we talk about *Innovation Without Change*, and there is also a reason why we are called Credence MedSystems. It's about the credibility that you build with partners that trust you, and that trust continues to grow over time.

> "This is easily the best engineering team I've ever worked with. They get customer wants and needs, they bring invention into development quickly, the answer is never "no" and inevitably they come back with a solution to a problem. It's really just a pleasure"

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John A. Merhige is Chief Commercial Officer at Credence MedSystems. Previously, he was Vice-President, Market Development at Sanofi BioSurgery. He came to Sanofi upon its acquisition of Pluromed in 2012, which John joined in its early stages and where he was a member of the executive management team. He led the commercial activities at Pluromed, which developed and commercialised rapid transition polymers for cardiovascular and other surgical procedures. Prior to Pluromed, John founded Prelude Devices to target early-stage medical device technologies for development and commercialisation. John is a member of PDA, MassMEDIC, MassBio and has served on the board of directors of the MedDev Group.

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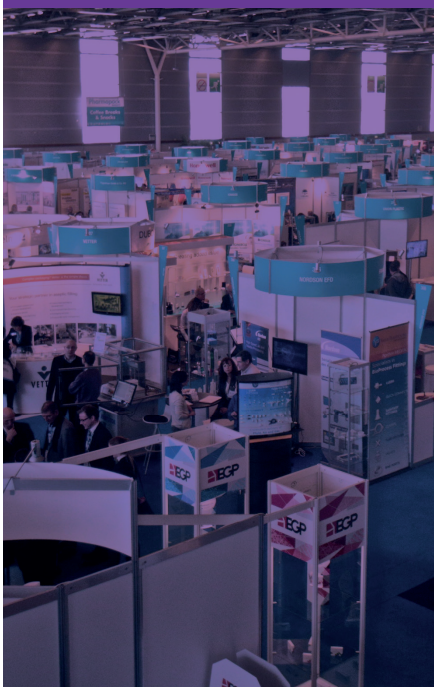

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UBM

A POLYMER-BASED PREFILLABLE SYRINGE SYSTEM TO MINIMISE RISK OF PROTEIN OXIDATION

Here, William Dierick, Director, Technology Development, Terumo Europe; and Koji Nakamura, PhD, Global D&D, Terumo Corporation, explore oxygen and free-radical mediated mechanisms of protein drug degradation within prefilled syringes, present research data, and suggest that using a deoxygenated packaging system to reduce or remove dissolved oxygen is an effective means of minimising oxygen-mediated degradation, and that steam sterilisation, as against e-beam, could be a means to reduce free radical-mediated degradation.

INTRODUCTION

In the global market, prefilled syringes are preferred as a parenteral drug container in providing various advantages such as ease of use, less overfill compared to vials, and minimising errors in clinical use.[1] The applications and interest for prefilled syringes as a primary drug container are increasing due to the heightened importance of biopharmaceuticals in parenteral drug development.[2] In 2014, the US FDA issued a Guidance for immunogenicity assessment for therapeutic protein drugs.[3] Section 8 of this Guidance addresses the considerations with regard to container closure interactions, indicating that these are more likely with prefilled syringes of therapeutic protein products. The FDA cites that the following are container closure considerations pertinent to immunogenicity: protein aggregation and denaturation related to silicone oil, glass and air interfaces, as well as glass delamination and leached materials from the container closure system.

Taking this into consideration, Terumo has developed a silicone oil-free (SOF) prefillable syringe system comprised of a cyclo olefin polymer (COP)-based syringe barrel and i-coating™ stopper. The Terumo i-coating™ technology is a proprietary coating technology applied to the plunger stoppers to reduce the risk of protein aggregation induced by silicone oil.[4,5] In addition, the i-coating™ technology provides consistent performance of the break-loose and glide forces when the product is stored for an extended time, therefore providing a repeatable and predictable performance not found in siliconised glass prefillable systems.[4-6]

Protein degradation due to oxidation is well known.[1] Dissolved oxygen occurs naturally in the drug product during the formulation and filling processes. Nitrogen blanketing and other techniques are often used to reduce the effect of dissolved oxygen in the drug product. Based on recent research, this article will show how using a system approach to designing a deoxygenating package, can minimise protein degradation due to the presence of oxygen.[6-8] In addition, we will show how free radicals created during sterilisation can further contribute to oxidation and degradation of protein drug products stored in a prefilled syringe system.[8,9]

DISSOLVED OXYGEN

Generally, the polymer-based prefilled syringe has a relatively higher gas permeability than glass prefilled syringe. Over time, this may lead to increasing levels of dissolved oxygen in the drug product even with nitrogen blanketing or the anti-oxidising agents in the drug formulation. Glass prefillable syringes are often considered more appropriate than polymer-based prefillable syringes in applications with oxygen sensitive drug products.[7,8,10]

Dissolved oxygen is one of the factors causing protein degradation through the oxidation pathway.[6-8] To prevent oxida-

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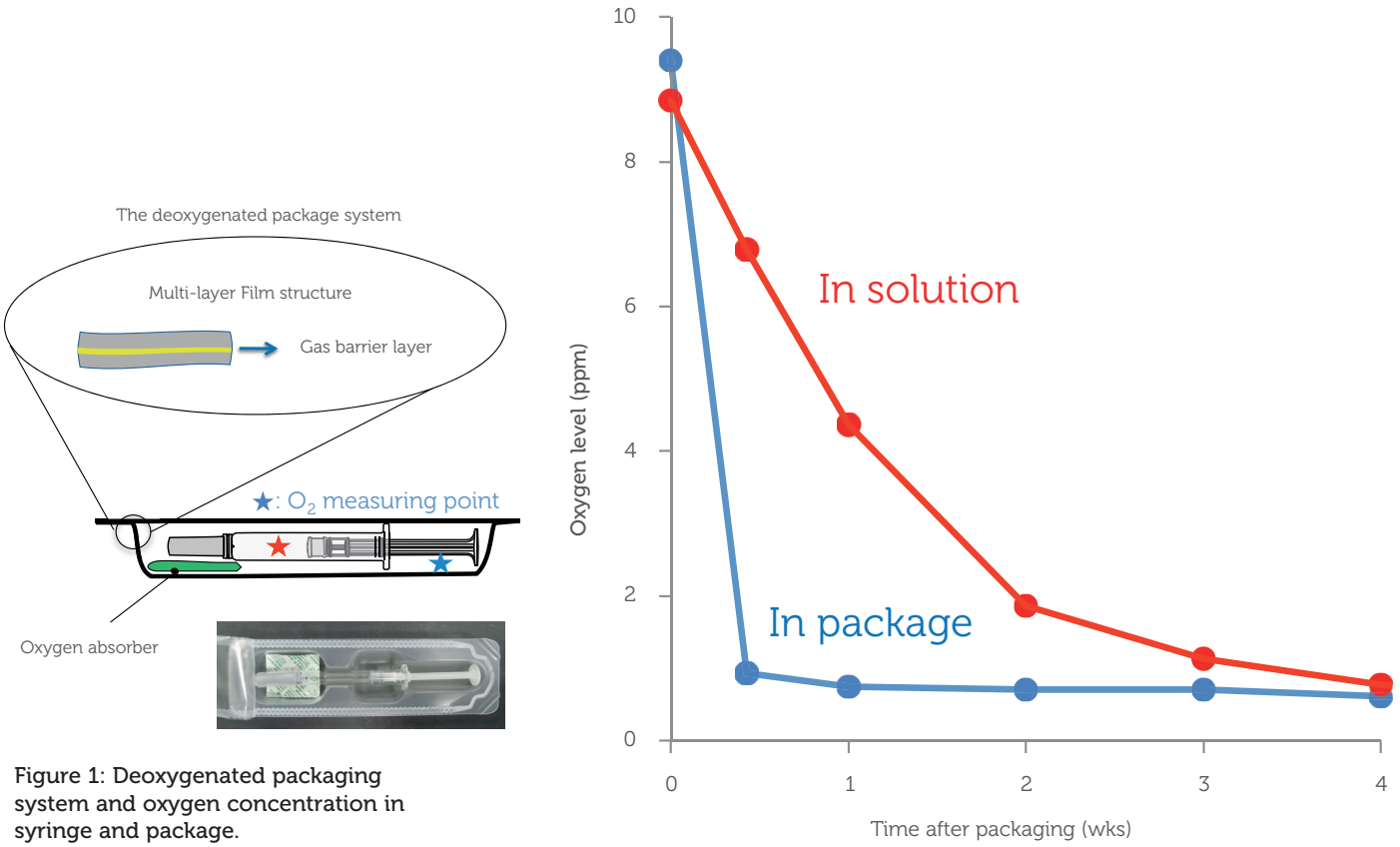

Figure 1: Deoxygenated packaging system and oxygen concentration in syringe and package.

tion of a drug product, measures should be taken, such as adding certain excipients into the drug formulation to control the oxygen level during manufacturing. An example of another method used is the Terumo prefilled syringe for multivitamins launched in 1999. This product is packaged into a deoxygenated packaging system composed of a low gas-permeable foil including an oxygen absorber as shown in Figure 1. Within this secondary packaging system, the oxygen level in the deoxygenated package decreased rapidly after sealing the package. Over time, the dissolved oxygen level in the solution within polymer-based prefilled syringe system also decreased.[6-8]

Figure 2 shows the comparative study between polymer-based prefilled syringes

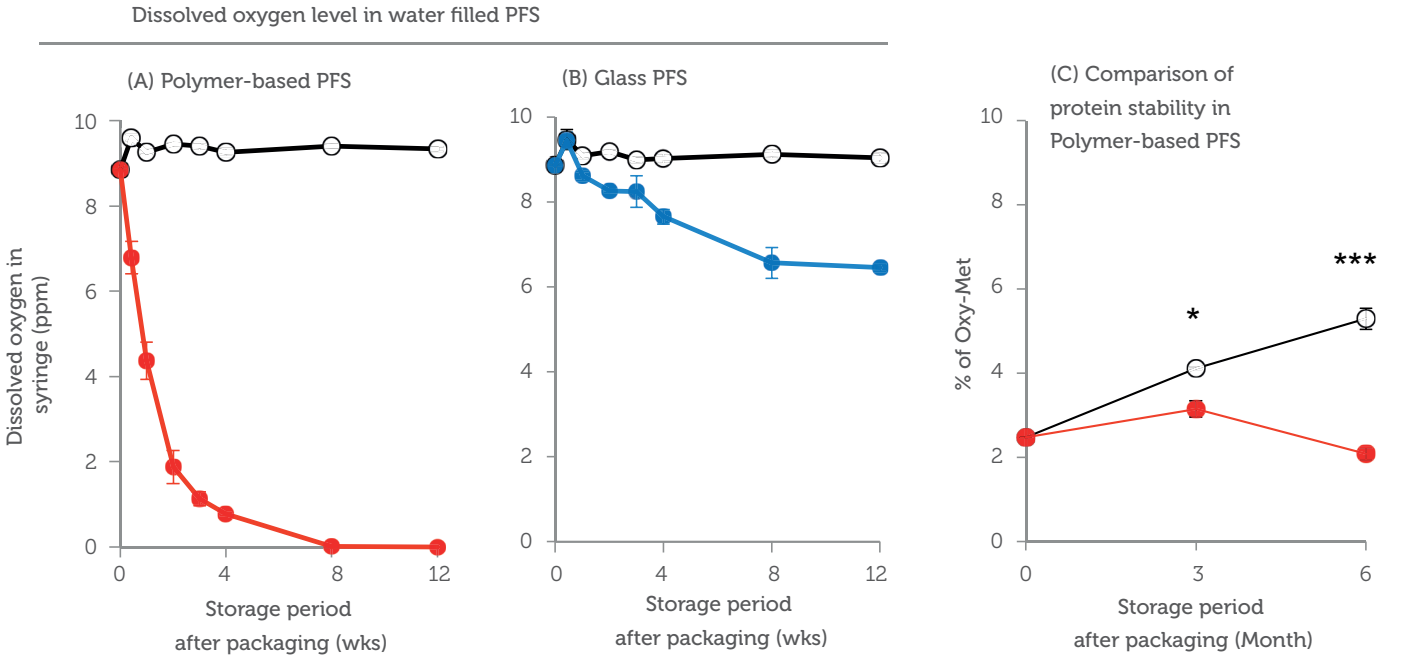

Figure 2: Reduction profile of dissolved oxygen in water filled (A) polymer-based PFS and (B) glass PFS, and (C) comparison of protein stability with and without deoxygenated packaging system. Open symbol: without deoxygenated packaging system, Closed symbol: with deoxygenated packaging system. (A), (B): Dissolved oxygen is measured by OXY-4 (PreSens). The value represents the mean +/- SD (n=3). (C) Data represents the mean +/- S.D. (n=3). *: $p < 0.05$, **: $p < 0.01$, ***: $p < 0.001$ against data from deoxygenated packaging system.

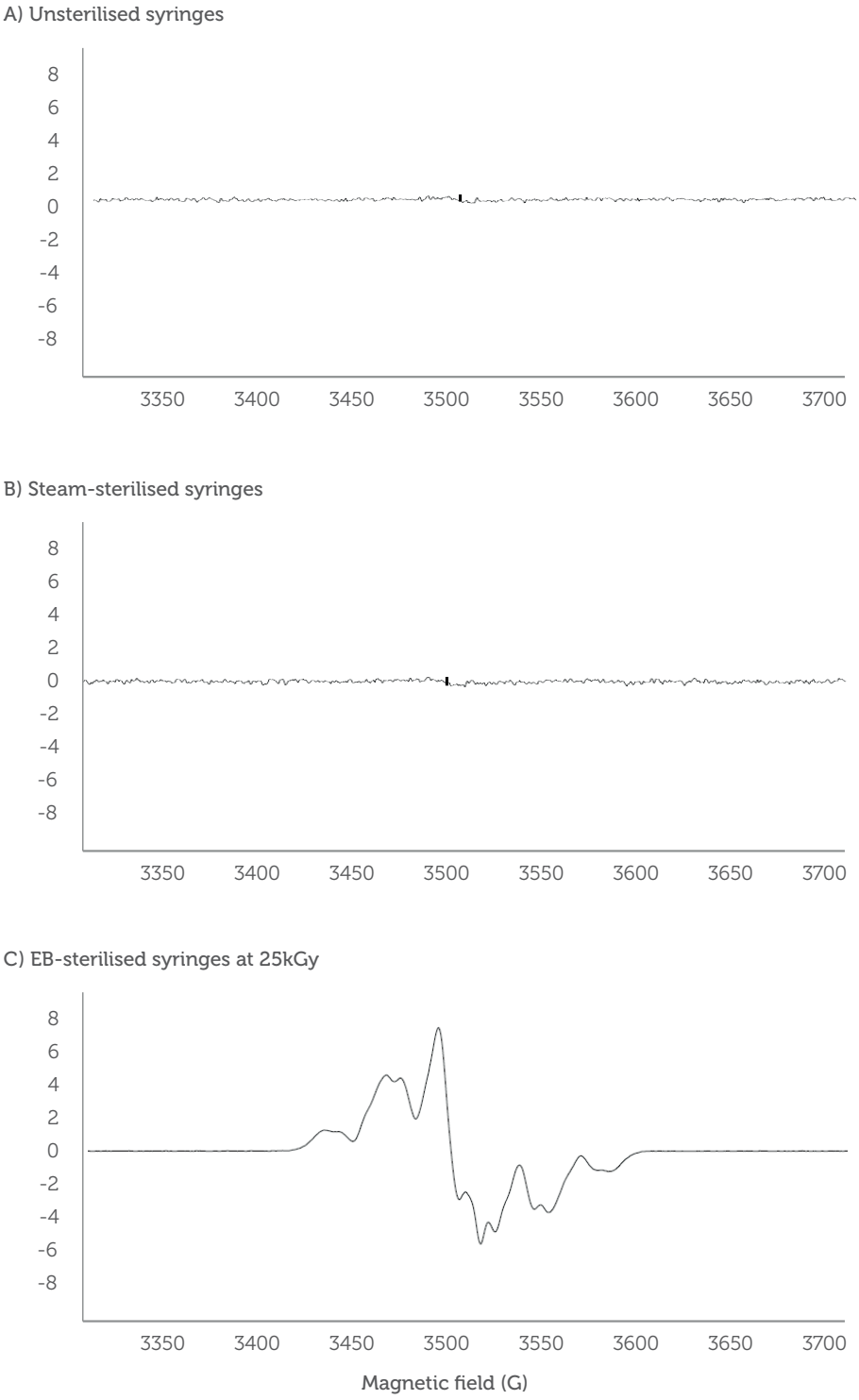

Figure 3: Typical ESR spectra of (A) unsterilised syringe; (B) steam-sterilised syringe; and (C) EB-sterilised syringe at 25 kGy.

and glass prefillable syringes packed with or without the use of a deoxygenated packaging system. With deoxygenated packaging systems, the dissolved oxygen level within the polymer-based prefilled syringes dramatically decreased compared to the non-deoxygenated (A). This decrease in dissolved oxygen within the glass prefilled syringes, irrespective of the deoxygenated packaging system, was not observed (B). To show the effectiveness of the proposed deoxygenated packaging system, a comparative study was also conducted to demonstrate the difference in protein oxidation between polymer-based prefilled syringes packed with or without a deoxygenated packaging system (C). As a result, the protein drug without the deoxygenated packaging system revealed a significantly higher Met-Oxy ratio than the samples kept within the deoxygenated packaging system at all time points, except time zero.

> "A deoxygenated packaging system for polymer-based prefilled syringes is very useful for protein drug products that are vulnerable to degradation by dissolved oxygen"

Through our research, this concept has been proven: a deoxygenated packaging system for polymer-based prefilled syringes is very useful for protein drug products that are vulnerable to degradation by dissolved oxygen.

The differences of oxygen elimination between glass- and polymer-based prefilled syringes are considered to be as a result of the difference in gas permeability characteristics. Gas permeability is extremely low for glass prefilled syringes compared to polymer-based prefilled syringes. Only polymer-based prefilled syringes can achieve oxygen control within a deoxygenated packaging system, while maintaining adequate container closure.[6-8]

RADICALS FROM STERILISATION BY IRRADIATION

Decomposition of protein drug products may result in unexpected side effects and/or reduced effectiveness, therefore controlling and preserving the product quality is of paramount importance.[3] Polymer-based prefillable syringe barrels can be sterilised by ethylene oxide gas, steam, and irradiation. It is generally understood that radicals are generated by irradiation, but so far there are few reports that show the impact of radical formation on protein stability. Sterile, single-use syringes (also called disposable syringes) are often sterilised by gamma or electron-beam (EB) sterilisation. There is minimal risk from the effect of radicals on drug stability because the drug solution taken into these syringes have a relatively short contact period within the syringe and are immediately administered to patients. However, in the case of prefilled syringe systems intended as the primary container for medicinal products, the storage period is substantially longer and generated radicals may have a greater impact on drug product quality.[8-9]

The amount of generated radicals can be quantitatively calculated based on the

results of electron spin resonance (ESR) according to the method as previously reported.[11-12] Typical spectra of ESR analysis on the polymer-based prefillable syringe after the EB sterilisation at 25 kGy or steam sterilisation are shown in Figure 3. The results reveal no significant differences between ESR spectra of unsterilised (A) and steam-sterilised syringes (B). However, considerable differences in ESR spectra are observed between the steam-sterilised (B) and EB-sterilised syringes (C).

The results obtained by calculating the generated radicals based on the ESR spectra are shown in Figure 4. These findings suggest that the EB sterilisation causes radical generation in polymer-based prefilled syringes.

The effects of such radicals from EB sterilisation on protein oxidation have been investigated in experiments with erythropoietin; tests conducted at conditions of 25 °C and 65% RH. Figure 5 shows the profile of observed Oxy-Met in erythropoietin solution after filled into EB-sterilised syringes and steam-sterilised syringes. The Oxy-Met level in the steam-sterilised syringes is similar to the non-sterilised syringes whereas the EB-sterilised syringes show an enhanced yielding of Oxy-Met compared with the steam-sterilised syringes. This difference in protein stability is attributed to the presence of radicals on the polymer-based syringes.

Furthermore, material analysis by Fourier transform-infrared spectroscopy (FTIR), and electron spectroscopy for chemical analysis (ESCA), was also conducted. Alongside the ESR analysis, FTIR spectra obtained in EB-sterilised syringes differ from that of steam-sterilised syringes. FTIR spectra obtained in steam-sterilised syringes resemble that of unsterilised syringes (Figure 6).

"In the case of prefilled syringe systems intended as the primary container for medicinal products, the storage period is substantially longer and generated radicals may have a greater impact on drug product quality"

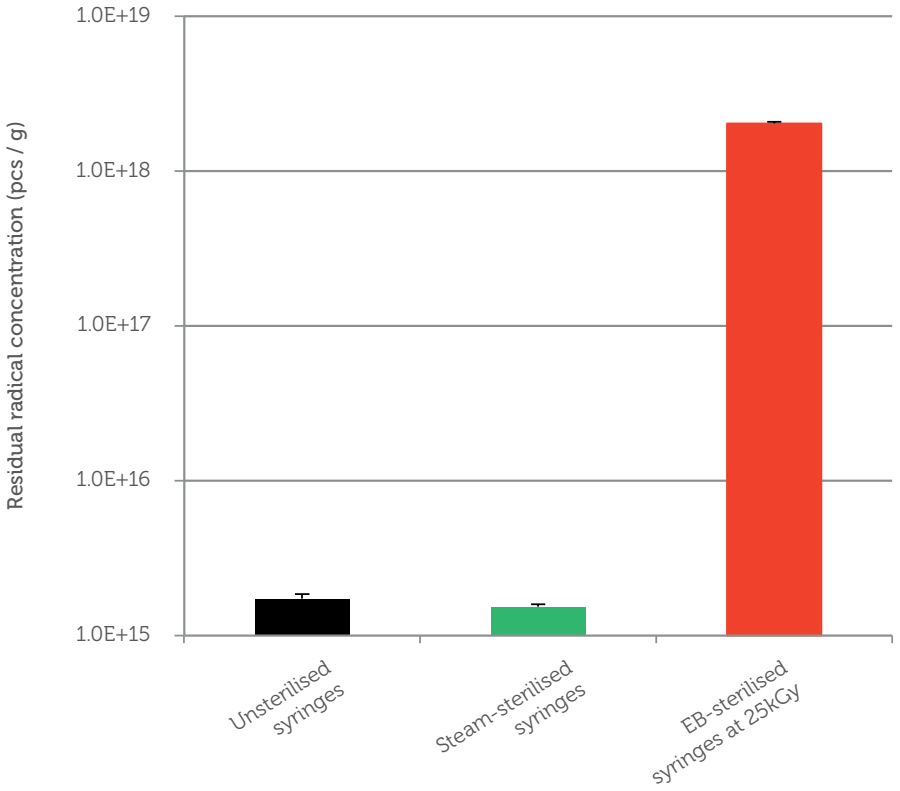

Figure 4: Residual radical amounts in unsterilised syringe, steam-sterilised syringe, and EB-sterilised syringe at 25 kGy. The data are presented as the mean +/- SD (n = 3).

Figure 7 summarises the chemical identification result based on the analysis by FTIR and ESCA. This result suggests that polymer barrel material (Cyclic Olefin Polymer, COP) is also subject to oxidation since C=O and C-O bonds are identified only from EB-sterilised

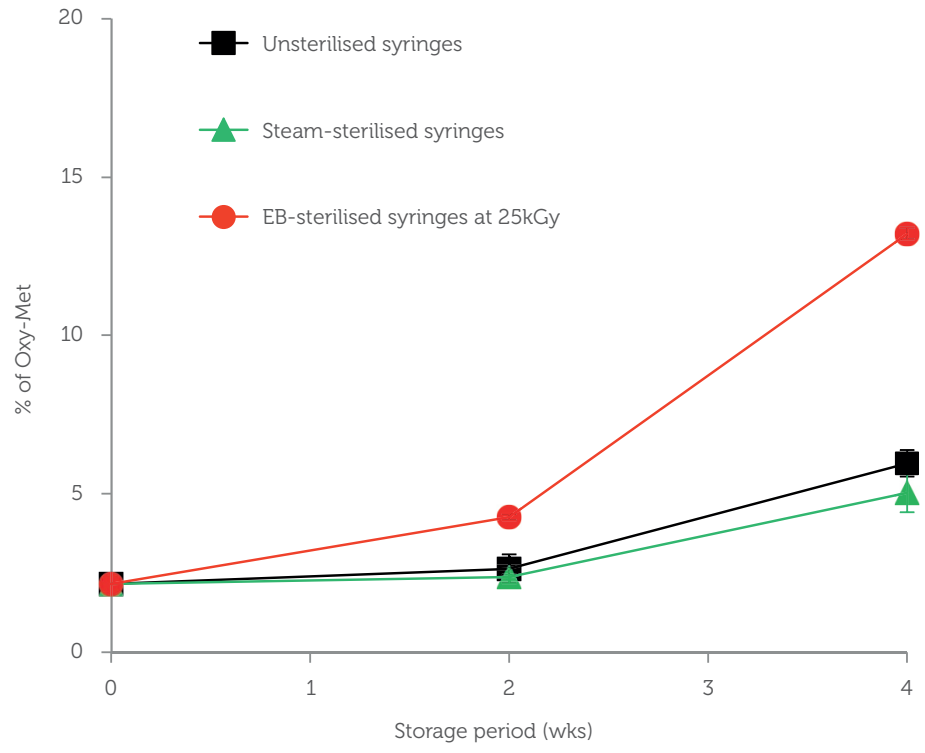

Figure 5: Difference in Oxy-Met production during the storage of erythropoietin filled into unsterilised syringe (square), steam-sterilised syringe (triangle), and EB-sterilised syringe at 25 kGy (circle) at 25°C and 65% RH. The data are represented as the mean +/- SD (n = 3).

Figure 6: IR spectra of (A) unsterilised syringe; (B) steam-sterilised syringe; and (C) EB-sterilised syringe at 25 kGy. Data are results of a single measurement.

syringes. These findings suggest that steam sterilisation is the preferred sterilisation method for polymer-based prefilled syringe systems, due to lower radical generation and therefore no enhancement of protein oxidation.

CONCLUSIONS

The root cause of protein oxidation have been identified as being dissolved oxygen within the drug product and the effect from radicals generated within polymer-based prefilled syringes by EB sterilisation.

Oxidation reaction due to dissolved oxygen can be minimised by controlling the oxygen content by reduction or complete removal of the dissolved oxygen using a deoxygenated packaging system. Radical generation within polymer-based prefillable syringes due to irradiation is not well known and is presented here for discussion. This presents a very important and critical aspect compared with the control of dissolved oxygen because it was thought that any sterilisation method for prefillable syringes was acceptable and would not result in reduction of product quality.

Through our experiments and results, the main oxidation pathway of a protein has been identified as dissolved oxygen and radical generation within polymer-based prefillable syringes. This report also demonstrates several solutions for controlling oxidation by means of applying a deoxygenated packaging system as well as utilising steam sterilisation as a method of sterilisation for polymer-based prefillable syringes.

(Note: research data in this article are on file at Terumo and are based on earlier publications from Terumo as referenced).

	Identified chemical bond	
	C=O bonding	C-O bonding
Unsterilised syringe	NONE	NONE
Steam-sterilised syringe	NONE	NONE
EB-sterilised syringe	IDENTIFIED (FTIR, ESCA)	IDENTIFIED (ESCA)

Figure 7: Summary of Chemical Identification Results Based on FTIR & ESCA analysis.

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COMPANY PROFILE: SPECIALTY COATING SYSTEMS

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As the global leader in delivering innovative Parylene coating solutions for advanced medical technologies, manufacturers have continually turned to SCS for planning, development, engineering and application of thin-film Parylene polymer coatings to their critical components.

Our team consists of the world's foremost Parylene specialists working in state-of-the-art laboratory facilities. Our strict quality control systems across eleven coating facilities worldwide ensure that all SCS customers experience the most innovative, precise and consistent coating processes.

OUR HERITAGE

SCS dates back to the 1970s when Parylene conformal coatings were first commercialised due to William F. Gorham's work at Union Carbide Corporation (UCC), now a subsidiary of Dow. In 1971, Nova Tran Corporation was established in Clear Lake, WI, US, having purchased a license agreement from UCC to be one of the world's first Parylene service providers. Union Carbide Corporation purchased Nova Tran in 1984 and in 1991, Nova Tran, along with several other companies, were combined into a new company called Specialty Coating Systems (SCS). Union Carbide transferred all of the original information and patents regarding the development of Parylene to SCS. With our global headquarters now located in Indianapolis, IN, US (see photo), we are proud of our heritage, which has afforded us unprecedented coating and applications expertise.

INNOVATIVE PRODUCTS FOR THE MEDICAL & PHARMA INDUSTRIES

Ultra-thin and pinhole-free, SCS Parylenes offer exceptional properties for medical device protection. We couple the properties of Parylene with our years of experience, vast technology and worldwide resources to provide the industry with reliable coatings and services. The benefits of SCS Parylene include:

- Biocompatibility and biostability
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- Ultra-thin, conformal coating of all exposed surfaces
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- Superior chemical, moisture and electrical barrier.

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HOW WE CAN HELP YOU MAKE SAFER AND BETTER DEVICES

SCS can apply Parylene coatings to virtually any surface material, including metal, elastomer, plastic, glass, ceramic and paper.

Specialty Coating Systems' worldwide headquarters in Indianapolis, IN, US.

The thickness of a Parylene coating can range from a few hundred angstroms to several mils. Parylene polymerises as a uniform, thin-film coating that conforms to all surfaces, edges and crevices of a substrate, including the interior of tubing, without blocking orifices, adding dimension or weight. Because Parylene is not a liquid, the coating suffers none of the meniscus and edge effects of conventional liquid coatings. As a result of its ultra-thin application, Parylene adds very little dimension or mass to critical, weight-sensitive components.

Numerous medical devices and device components benefit from Parylene coatings, including syringe components, needles, stents, electrosurgical tools, cochlear and

ocular implants, ingestible devices, pacemakers, and elastomeric components.

PHARMACEUTICAL APPLICATIONS: WHY PARYLENE STANDS OUT

Shelf-life is important for all medications, for prefilled syringes as well as pharmaceuticals in vials and bottles. For these, the more aggressive chemicals tend to attack not only the containers, but can cause unwanted chemicals to be extracted from the container material into the drug itself. Parylene can prevent this. It is an excellent barrier coating, protecting the container, including caps and seals, and also protecting the drug from any unwanted leaching or extractions.

Some prefilled syringes have sealing mechanisms to ensure needle sterility and to prevent premature drug dispensing. These seals can occasionally form a very tight bond as it sits on the shelf. The self-seal can be difficult to break. Coating these components with Parylene before assembly helps prevent seal bonding. In this case, Parylene acts as a release agent allowing the sealing material to release easily when needed.

AT SCS, EVERY CUSTOMER MATTERS

Our worldwide resources include highly experienced sales engineers and expert manufacturing personnel working in eleven state-of-the-art coating facilities around the globe.

The following is an overview of the activities, standards and certifications to which SCS and/or SCS Parylene coatings comply:

- AS9100C certification
- US FDA Device and Drug Master Files
- Notified Bodies and Accredited Third Parties co-ordination
- ISO 10993 biological evaluations and certifications
- USP Class VI certification
- ISO 14644 cleanrooms.

Every customer has unique product and performance specifications that must be met. Our experience and expertise are leveraged on every project in order to meet the most challenging specifications and quality requirements.

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COMPANY PROFILE: HASELMEIER

HASELMEIER
Drug Delivery. Tailormade.

User Focus

At Haselmeier, our mission is to create products enabling a convenient and comfortable experience. This is why patient feedback is integrated early in our device designs. Early concepts are prototyped for testing and Human Factors studies to capture the handling needs and skills of potential users. This knowledge is integrated into the device design to provide successful administration of the drug product and a positive user experience.

Haselmeier offers a range of early-stage activities:

- Think-tank discussions and paper concepts
- Detailed product concepts and industrial designs
- Detailed user handling review and risk-analysis
- Prototyping of initial concepts up to functional devices
- User focus groups and human factors studies for concept and prototype evaluations
- Detailed user requirements and product design specifications based on selected concept.

Bridge to Market

Successful development and industrialisation of drug delivery devices is dependent upon the understanding and execution of today's technical, regulatory and operational requirements. At Haselmeier we provide integrated design, development and industrialisation services to help you bridge your serial product into the market. Our qualified design control process, certified quality system, regulatory expertise, solid network of partners and strong manufacturing operations are all designed to achieve your expectations. Together we enable a smooth market introduction for your commercial drug delivery device.

Haselmeier's commercial development and industrialisation services include:

- Concept transfer into detailed User Requirements and Product Design Specifications
- A certified Design Control Process and Quality System
- Design verification, product and process validation processes
- Regulatory expertise to support your approval strategy
- Controlled design-to-manufacturing transfer, verification and validation.

> "Successful development and industrialisation of drug delivery devices is dependent upon the understanding and execution of today's technical, regulatory and operational requirements"

Manufacturing & LifeCycle Partner

We understand that each customer has individual and specific requirements for their product. Regardless of your requirements, Haselmeier applies the highest quality standard for manufacturing your drug delivery device to ensure a reliable and reproducible manufacturing and quality process. We work continuously with our customers to identify product improvements at all stages of the product's lifecycle to provide a safe and state-of-the art drug delivery device.

Haselmeier provides flexible, reliable, manufacturing and lifecycle management:

- Certified and modern production facilities and manufacturing processes
- Qualified and well trained personnel
- A strong network of sub-suppliers and manufacturing partners
- Continuous Engineering and product improvement programme
- Innovation meetings to identify next product generation.

PLATFORM & PRODUCTS

The Haselmeier Axis-D Pen System (Figure 1) is a disposable, variable-dose injection device designed for the use with a 3 mL cartridge. The elegant and compact Axis-D Pen System is available as a high quality plastic version.

- No or minimal priming
- Accurate dose reading with sliding window
- No rotating outer components
- Protected dose scale.

The Haselmeier i-pen (Figure 2) is a reusable, variable dose injection device for use with a standard 3 mL cartridge. The

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Working together to inspire your patients

At Haselmeier we work in close cooperation with our pharmaceutical partners to create and deliver the safest and easiest to use injection devices for their patients.

Our proven device platforms, world leading engineering and global manufacturing capabilities combined with an intense focus on patients provides our partners with a total product solution that helps improve patients' lives.

Experience **User Focus, Bridge to Market** and **Manufacturing & LifeCycle Partner** here:

HASELMEIER

Drug Delivery. Tailormade.

COMPANY PROFILE: HASELMEIER {... CONTINUED}

"We understand that each customer has individual and specific requirements for their product"

i-pen features an elegant non-medical design which is the result of extensive research and patient testing.

- Dose adjustment from 0.01 mL to 0.6 mL per injection
- Compact size enables easy handling and portability
- Large, easy-to-read dose indicator
- All metal outer body.

The i-pen² (Figure 3) is a reusable, variable-dose injection device for use with a standard 3ml cartridge. The i-pen² was specifically created to provide a high-quality pen at economic cost.

- Dose adjustment from 0.01 mL to 0.6 mL per injection
- Compact size enables easy handling and portability
- Large, easy-to-read dose indicator
- All plastic components

The Softpen (Figure 4) is a fully automatic, reusable injection device featuring Haselmeier's patented hidden needle design. Upon depressing the clip on the pen, the needle automatically enters the subcutaneous tissue followed by delivery of the solution.

- Fully automatic needle insertion and injection
- Needle is hidden prior to and during injection
- Multiple injections from single 3ml cartridge.

The Haselmeier disposable Penlet (Figure 5) is a fully automatic, fixed dose injection device designed for use with a standard 3ml cartridge. Upon depressing the clip on the pen, the needle automatically enters the subcutaneous tissue, which is followed by delivery of the solution.

- Ready for use by the patient and no dose adjustment required
- Fully automatic needle insertion and injection
- Needle is hidden prior to and during injection.

Figure 1: The Axis-D Pen System – disposable, variable-dose injection device designed for the use with a 3 mL cartridge.

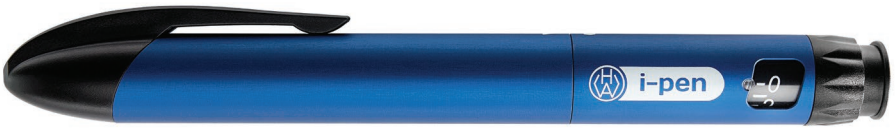

Figure 2: The i-pen – reusable, variable-dose injection device for use with a standard 3 mL cartridge.

Figure 3: The i-pen² is a reusable, variable-dose injection device for use with a standard 3 mL cartridge.

Figure 4: The Softpen – a fully automatic, reusable injection device featuring Haselmeier's patented hidden needle design.

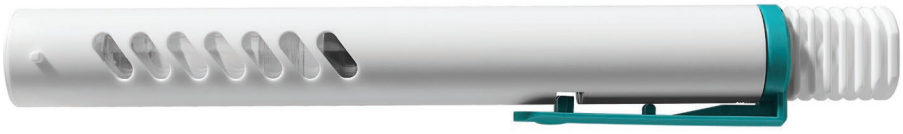

Figure 5: The Penlet is a fully automatic, fixed-dose injection device

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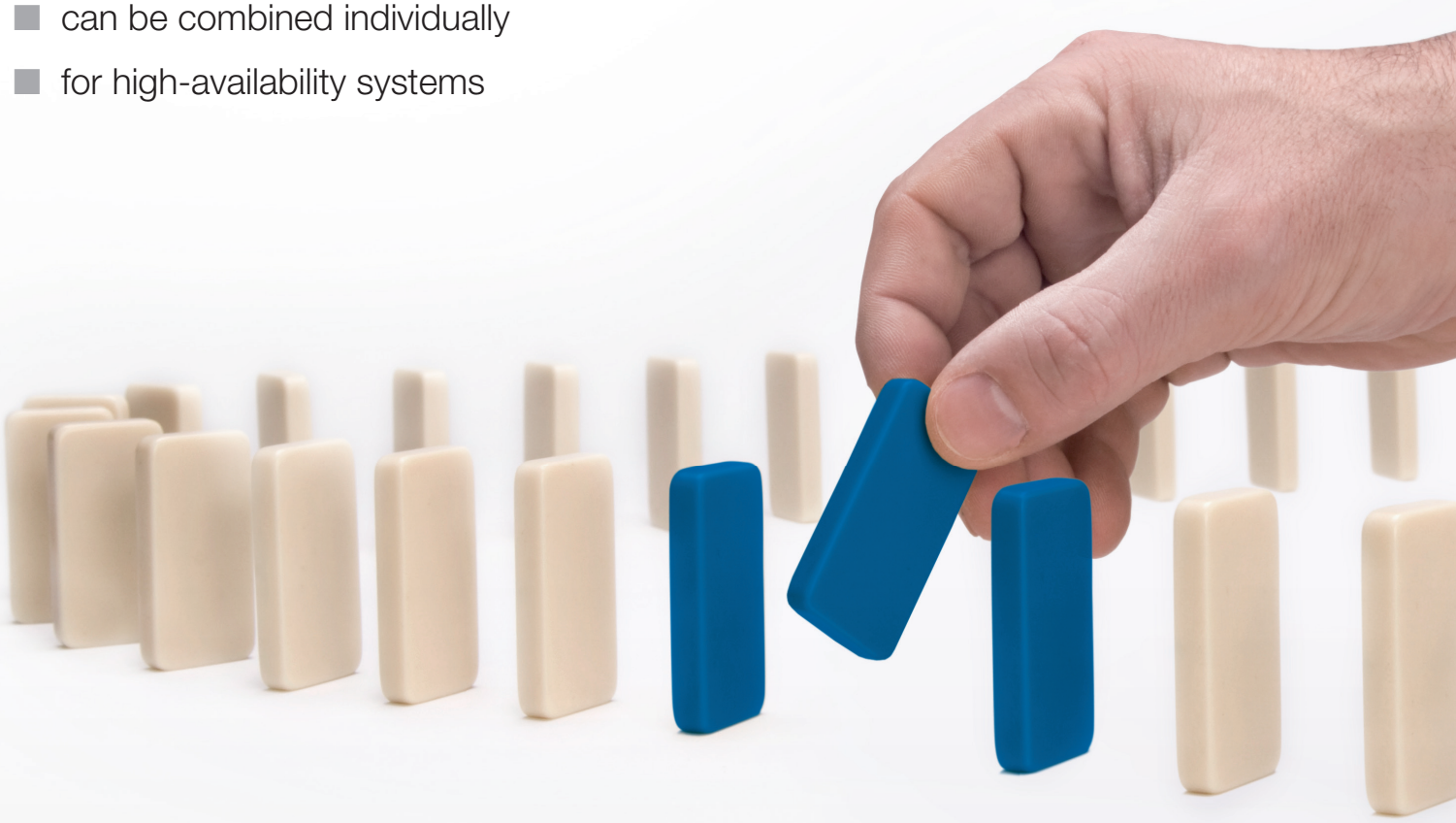

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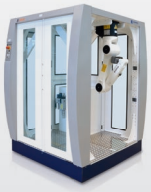

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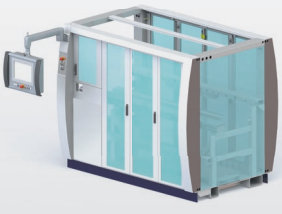

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COMBINING INDIVIDUAL DESIGNS WITH THE BENEFITS OF A PROVEN PLATFORM PRODUCT

In this article, Orfeo Niedermann, Business Development Director, Ypsomed Delivery Systems, gives insights into the requirements on modern self-injection devices and explains how the advantages of a proven platform product – short timelines, low risk and attractive costs – can be combined with the implementation of an individual industrial design, providing differentiation or tailoring to a specific patient group.

With the large number of new biologics, and the surge in biosimilar product launches, the demand for devices for the subcutaneous self-injection of biopharmaceuticals continues to grow and develop. New devices focus on simpler self-injection procedures and improved patient adherence for auto injectors, pens and larger volume injectors.

As the number of devices reaching the market increases, pharmaceutical and biotech companies are looking to source state-of-the-art devices that are available quickly and at low risk for both clinical trials and commercial launch. A self-injection device should provide product differentiation through improved human factors and increased safety compared to vial-syringe and prefilled syringe product presentations. At the same time, pharma companies strive to differentiate their own self-injection device from devices used by competitors. Meeting these objectives can be challenging for pharma companies and device manufacturers.

> "Ypsomed has decoupled the development of new platform products from the customer project and thereby moved risk in-house to cover platform development and installation of manufacturing infrastructure"

REQUIREMENTS FOR SELF-INJECTION DEVICES

Simple and safe use are key requirements of modern self-injection devices. Ypsomed uses a human centred design approach to create new concepts for injection devices. During the development process, multiple rounds of formative human factors studies provide feedback to improve the concept to make the use of the device easier and to support the patient's adherence to the therapy.

Typically the patient prefers a device that is discrete and compact. It should require only a few operation steps, may have a shielded needle and offer convenient disposal. Furthermore, the device may have to provide simple dose setting when needed and has to fulfil dose accuracy and other requirements from the applicable standards.

Testing of the final device in Phase III studies calls for quick availability of devices shortly after the decision has been made that a device shall be used for commercial launch. All of the above factors are important for the successful development and launch of the final combination product.

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Figure 1: YpsoMate® – the 2-step auto injector in the original square shape.

Figure 2: YpsoMate® auto injector in second design variant in round shape and specific colour.

LEVERAGING PLATFORM PRODUCTS

As an answer to these requirements, Ypsomed has built up comprehensive platform products, which allow faster and simpler development projects while minimising project risks and shortening time to market. To achieve this, Ypsomed has decoupled the development of new platform products from the customer project and thereby moved risk in-house to cover platform development and installation of manufacturing infrastructure. In short the benefits of starting a device project of a platform product are:

- Prototype devices available off-the-shelf for handling studies
- Reduced project risks by building device projects on proven technology
- Established patent position
- Devices quickly available for clinical trials
- Short and reliable commercial project timeline
- Reduced project cost and unit price.

A highly successful platform product in Ypsomed's portfolio is YpsoMate – the two-step auto injector based on a prefilled syringe (Figure 1). It serves patients with an easy and convenient two-step automatic injection.

The patient pulls off the cap to remove the sterile needle shield from the prefilled syringe and then pushes the auto injector onto the skin to trigger the injection. The operation is simple and safe and does not involve any additional button-activated steps. An additional activation button requires more user steps and is often inconvenient to perform for patient groups with limited dexterity. This was an important finding in Ypsomed's human-centred design process and a key reason for the success of two-step auto injectors.

The YpsoMate auto injector signals the start as well as the completion of the injection through clearly audible clicks. In parallel the patient can observe the injection progress in the large viewing window. During the injection the needle remains hidden and is shielded after use to prevent needle stick injuries. All these features are built into a compact housing that fits nicely into the palm of the hand and is easy to dispose of.

CUSTOMISATION IS KEY

A modern and successful self-injection device needs to be adapted to the selected primary container, to the formulation characteristics such as drug volume and viscosity and to the needle insertion depth as required for certain therapies. Ypsomed has therefore designed the YpsoMate auto injector to be compatible with all available 1 mL long syringes made of glass or COP and for a range of needle shields from all major suppliers whether rigid or flexible.

The YpsoMate platform product is also easily adapted to the drug product to meet specific fill levels and viscosities in conjunction with the selected needle gauge and needle penetration depth.

DIFFERENTATION THROUGH INDIVIDUAL INDUSTRIAL DESIGNS

However, for certain products and indications there might be a strong demand for a unique product to differentiate from competitor products. Ypsomed offers YpsoMate in two standard designs (Figures 1 & 2) that are ergonomically proven and tested. In addition, different colours and colour combinations can be selected.

If specific patient groups, or demand for differentiation in a specific market, calls for a completely new outer shape Ypsomed offers the new device version, YpsoMate Design, that still relies on the proven YpsoMate technology. The technical concept of the outer shell structure of YpsoMate Design allows for more freedom to generate a unique, pleasing and ergonomically optimised shape. In addition to the possibility of designing free-form surfaces it is also possible to use different surface materials to improve the grip and to emphasise how to hold and use the device (Figure 3).

Figure 3: Example of YpsoMate® Design – a version of the proven YpsoMate® platform auto injector with a fully customisable, individual industrial design.

Figure 4: Flexible assembly line for fully customised YpsoMate® auto injectors at one of Ypsomed's Swiss manufacturing sites.

In short, with YpsoMate Design it is possible to manufacture a fully customised auto injector with specific technical characteristics including an individual outer shape on a fully automated manufacturing line. This solution provides the pharma company with a very specific and exclusive device while still leveraging all the advantages of the platform product.

EFFICIENT AND FLEXIBLE MANUFACTURING

To keep the timeline short and project upfront investment low, Ypsomed has invested in automated manufacturing capacity for the YpsoMate platform product (Figure 4). This allows customers to access and source the device at a fraction of the overall cost compared to investing in bespoke manufacturing infrastructure.

The fully automated line consists of four individual cells that are linked with a conveying system. The components, which are all moulded at the same site in Switzerland, as well as the special springs, are delivered into the machine with feeding systems. The assembly equipment inspects the parts inline and generates two sub-assemblies that are nested to reduce packaging space before being arranged into trays and stacked for shipment to the final-assembly site. All standard housing versions as well as the YpsoMate Design inner housing version are assembled on the same fully automated assembly line. The machine is interfaced with Ypsomed's SAP system and all parts entering the machine are traceable in the resulting sub-assemblies.

FLEXIBILITY & SUPPORT FOR DRUG & DEVICE FINAL ASSEMBLY

For the drug and device end assembly process, Ypsomed fully supports its pharma partners to help select the best possible logistics for their product and supply chain. To support the final device assembly step, Ypsomed works with a select number of renowned assembly equipment manufacturers to prepare machine concepts for manual, semi-automatic and fully automatic equipment for different capacity needs. This allows the pharma company to pursue the appropriate final assembly strategy objectively in combination with the inspection, labelling and packaging of the final combination product.

When using YpsoMate Design, the equipment is additionally configured to assemble the outer shells around the auto injector housing.

> "The technical concept of the outer shell structure of YpsoMate Design allows for more freedom to generate a unique, pleasing and ergonomically optimised shape"

CONCLUSION

The demand for a specific and exclusive self-injection device is not incompatible with the clear need for easy to access proven technology. Based on a well thought out design, that considered a broad range of customisation during early development of the technical concept as well as during the parallel development of the manufacturing process, the YpsoMate auto injector platform product can meet virtually all biopharmaceutical needs for a simple and attractive yet affordable self-injection device.

ABOUT YDS – YPSOMED DELIVERY SYSTEMS

Ypsomed is the leading independent developer and manufacturer of innovative auto injector and pen injector systems for self-administration. The customisable product platforms cover auto injectors for prefilled syringes in 1 mL and 2.25 mL format, disposable pens for 3 mL and 1.5 mL cartridges, re-usable pens that include automated injection mechanisms and easy-to-use injection devices for drugs in dual-chamber cartridges such as lyophilised drugs. Unique click-on needles and infusion sets complement the broad self-injection systems product portfolio. Ypsomed provides its partners excellent technological expertise and full regulatory support for the device relevant aspects of the registration process.

The injection systems are developed and manufactured in Switzerland with strong in-house competencies covering concept and product development, tool-making, injection moulding and automated assembly. Ypsomed is ISO 13485 certified and all processes are run according to design control and cGMP guidelines with operational QA/QC experts on-site at each location. Ypsomed's US FDA-registered manufacturing facilities are regularly inspected by both pharma customers and regulatory agencies and supply devices for global markets including US, Europe, Japan, China and India. Ypsomed has more than 30 years of experience and well-established working relationships with numerous leading pharma and biotech companies.

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February 2016	Prefilled Syringes	January 11th
March 2016	Transdermal Delivery & Microneedles	February 8th
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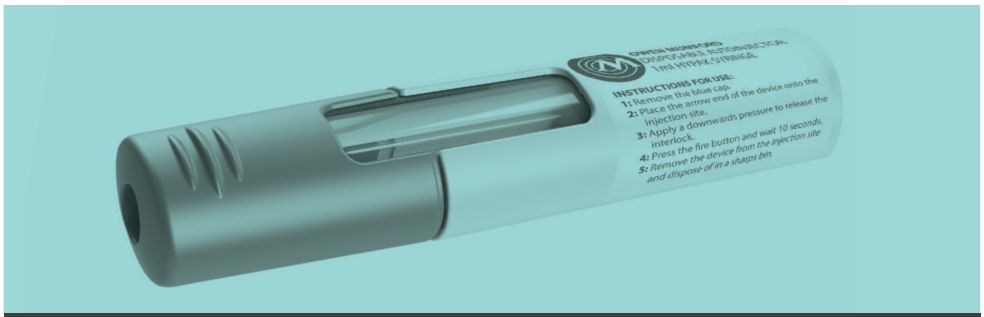

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PUTTING **LIFE** INTO **TECHNOLOGY**

DELIVERING VALUE FOR INJECTABLES: UNMET NEEDS, DEVICE SOLUTIONS & THERAPEUTIC OUTCOMES

What constitutes value today for an injectable drug or vaccine? That's a question increasingly being asked by patients, prescribers and payers when it comes to the selection and use of injectable therapies. While upfront price will always be important, there are multiple other factors now being used by healthcare stakeholders to determine how a particular brand of injectable therapy should be valued against its competition. This article, from Stephen Allan, Senior Vice-President, Strategic Planning, Unilife Corporation, examines why pharmaceutical companies are leveraging innovative delivery systems to enhance and differentiate their injectable products so that they can generate powerful value-based healthcare outcomes amongst payers, prescribers and patients.

GENERATING VALUE-BASED HEALTHCARE OUTCOMES VIA SAFER, SIMPLER, SMARTER DEVICES

Patients, prescribers and payers all have a key role to play in determining what brand of therapy will be used in the treatment of chronic diseases. Each of these stakeholder groups are motivated by a different set of factors that together can determine their brand of preference. For a pharmaceutical company seeking to optimise the use of its product against brand-name or biogeneric competitors to build or protect market share, it is important to pursue a multifaceted strategy that distinctly resonates across each of these audiences.

Promoting the distinctive molecular characteristics of a therapy alone is insufficient in this regard. In addition to demonstrating the pharmacokinetics and pharmacodynamics of an injectable molecule, pharmaceutical companies today must also showcase how it can enhance patient care, maximise therapy compliance and minimise healthcare costs. To maximise rates of preference and acceptability, a more holistic approach is required to showcase the value of the entire therapeutic package. In short, the value proposition for a therapy must extend beyond the drug itself to focus instead on the drug-device combination product.

"As prescribers are forced to manage an increasing number of patients within only a finite period of time, they will become even more attracted to the productivity gains and patient care enhancements attainable through the prescription of therapies leveraging smarter, simpler and more convenient devices"

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PATIENTS

Patients are becoming increasingly brand-aware regarding their therapy options, and highly influential in the selection of which brand they are prescribed. When it comes to selecting one competing brand of therapy against another, drug delivery systems are becoming a central factor in the decision making process.

Safety, simplicity and convenience of use are all of paramount importance from a patient perspective. How does the therapy fit within a patient's normal daily routine? Does it minimise the frequency of injection? Does it minimise the pain and discomfort associated with each injection? Is it so safe and simple to use that it minimises the risk of dosing error or drug wastage? Is it compact in size and ergonomic to hold? Can it be readily used in any environment such as the home, office, café or gym? Can it provide automatic reminders to the patient's smart phone on when the next dose is due, or preferred injection settings?

The capacity of a drug delivery device to address factors such as these fully can be critical in driving rates of patient preference and acceptability for a particular brand of injectable therapy, and enhance the likelihood of a pharmaceutical company building a long-term relationship with the patient.

PAYERS

Payers are vigorously encouraging the shift to the patient self-injection of injectable therapies to reduce healthcare costs and improve patient quality of life. However, a high rate of patient non-adherence across many chronic disease areas represents a significant financial drain on the healthcare systems.

To improve healthcare productivity and maximise rates of therapy adherence, many payers recognise that there are two core priorities in the supply and administration of injectable therapies for patient self-administration.

First, injectable therapies must be made as safe, simple and convenient as possible for patients to adhere to their medication regimes. As the primary interface between drug and patient, the ergonomic design, features and functionality of a drug delivery system are integral to the provision of patient-centric therapies that minimise common medication challenges including incorrect or missed doses. For categories such as wearable injectors, devices are even helping to enable or accelerate the treatment of chronic diseases outside of healthcare facilities.

Second, payers are seeking to gain better insight into how patients are utilising their prescribed therapies outside of healthcare facilities. In particular, the integration of Bluetooth LE within drug delivery systems such as auto injectors and wearable injectors represents a significant opportunity to leverage the power of data informatics. With access to real-time and historic data regarding compliance to a therapy regime, payers and prescribers will be better positioned to determine which particular therapy brand can deliver the most favourable long-term return on investment, regardless of upfront cost. Where multiple brand-name or biogeneric options are available, the value of this data may be instrumental in determining what level of market share a pharmaceutical company captures within the relevant therapy area.

PRESCRIBERS

Data informatics also represents a significant opportunity to bridge the gap between patients and prescribers. As one example, the prescription of an insulin pump with integrated Bluetooth connectivity to an insulin-dependent patient with Type 2 diabetes would allow an endocrinologist to tailor a therapy regime better, to help reach the patient's HbA1c goals. As another example, a prescriber with accurate, reliable access to a patient's specific history of injections will enable them correlate whether a recent adverse healthcare episode was caused by non-adherence or dosing error.

As prescribers are forced to manage an increasing number of patients within only a finite period of time, they will become even more attracted to the productivity gains and patient care enhancements attainable through the prescription of therapies leveraging smarter, simpler and more convenient devices. Pharmaceutical companies who are able to provide therapies in a device format that addresses these prescriber preferences will be in a strong position to build or protect market share against competitors with inferior data-driven outcomes.

CREATING VALUE FOR PHARMACEUTICAL CUSTOMERS

To better serve the needs of patients, payers and prescribers, and generate powerful brand differentiation for their injectable therapies against the competition, pharmaceutical companies are shifting rapidly to the use of innovative drug delivery systems to contain and administer injectable therapies. However, with each target therapeutic segment or drug indication having specific unmet or emerging needs, a one-size-fits-all approach to drug delivery systems is not feasible.

> "Unlike other companies where the business is predominantly based around materials or commodity components, Unilife was created from the ground up as a developer, manufacturer and supplier of sophisticated injectable drug delivery systems. It has a deep understanding of primary container technologies, and how they must be integrated into the effective production and functionality of a drug delivery system"

While each therapy segment and patient population has unique requirements, Unilife has experienced market success by pursuing a platform-based strategy whereby each device it develops must adhere to the following criteria:

- It must address significant unmet market needs
- It must be straightforward to industrialise by the pharmaceutical customer, and able to fit into standard drug filling and packaging systems
- It must minimise regulatory risk by utilising standard materials within the primary drug container
- It must be so safe, simple and convenient to use that it adds real value for patients, prescribers and payers
- It must be highly differentiated from the competition, and user-preferred; and
- It must be able to be sold at a price that represents real value for the pharmaceutical customer.

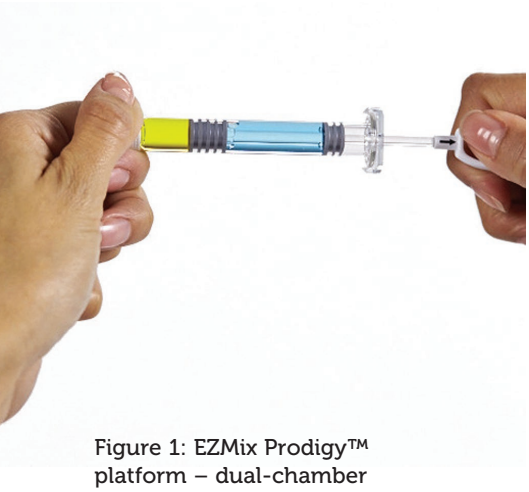

Figure 1: EZMix Prodigy™ platform – dual-chamber single-barrel prefilled syringes.

To demonstrate the flexibility of how this approach can be leveraged by pharmaceutical companies to enable, enhance and differentiate their injectable drugs across a range of therapy areas, this article provides examples of unmet needs and available device solutions for immuno-oncology, diabetes, vaccines and auto-immune diseases.

ADDING VALUE IN IMMUNO-ONCOLOGY

Therapeutic products to treat oncology have traditionally required IV infusion, with patients having to visit specialty care clinics or other healthcare facilities to receive treatment over several hours. For healthcare providers, the administration of such products is a complicated, time-intensive process with multiple pieces of equipment required to reconstitute and administer the dose. Patients receiving treatment also face a significant social and financial burden, with frequent facility visits, significant discomfort and high out-of-pocket costs. Payers are also acutely conscious of the high costs associated with IV infusion, including not only the purchase of the drug, but various ancillary pieces of equipment.

To support pharmaceutical companies seeking to address such unmet needs for oncology and immuno-oncology, Unilife has created a range of innovative platform technologies that can reduce cost and complexity, and potentially accelerate a shift in the place of treatment from the clinic to the home.

For drugs that require reconstitution and / or IV infusion, Unilife has created the EZMix Prodigy™ platform of dual-chamber single-barrel prefilled syringes (Figure 1). EZMix Prodigy products enable the automatic, ventless and orientation-free reconstitution or mixing of liquid-liquid combination products or lyophilised drugs up to 50 mL in volume with one simple step. The products can also be configured for universal connectivity with IV ports or needleless luer access devices.

Where a pharmaceutical company has an approved or pipeline immuno-oncology therapy, such as a monoclonal antibody, that is being targeted for subcutaneous administration, Unilife also has multiple delivery platforms available that can facilitate its simple and convenient administration by patients outside of healthcare facilities. In addition to prefilled syringes and smart-reusable auto injectors (see below), Unilife has developed a market-leading portfolio of wearable injectors to accommodate drugs requiring either dose volumes between 1 mL and 15 mL, or extended delivery periods over minutes or hours (Figure 2a and 2b). Prefilled, pre-assembled and supplied ready to administer a measured dose of drug at a preset rate and duration, Unilife's wearable injectors require only three steps to commence the initiation of therapy, and are equipped with an array of customisable features including Bluetooth LE connectivity.

ADDING VALUE IN INSULIN PUMPS

The current generation of insulin pumps has not been widely embraced within the Type 2 market, and only partially within the Type 1 market, due to device complexity, reimbursement constraints and high out-of-pocket cost for patients.

Upfront costs for durable insulin pumps can range up to US$7,000 (£4,530). There are then additional significant ongoing monthly costs for infusion sets and other peripherals. Disposable patch pump systems can be more expensive on a monthly basis. Such high upfront and monthly costs make insulin pumps less attractive for use within the Type 2 market. Insulin pumps are also bulky, and require intensive training before use. Multiple pieces of equipment are required, many of which require a separate prescription. Numerous steps are needed to begin insulin infusion therapy, with many more required to facilitate bolus delivery at mealtimes.

Unilife recognises that to gain broad acceptance across insulin-dependent people with diabetes, a patch pump technology must have minimal steps to commence basal therapy, as well as simple on-demand bolus delivery. It must be a fully integrated, prefilled insulin therapy solution that is so compact, convenient and discreet that it empowers patients to live a normal life by reducing the daily burden of diabetes treatment. Furthermore, it must minimise upfront and ongoing monthly costs for continuous insulin infusion therapy, so that it becomes as attractive for reimbursement as prefilled disposable insulin pens. And finally, just like insulin pens, it must leverage the established sales and distribution channels of diabetes market leaders.

Unilife has addressed these market requirements with the creation of Imperium™, the world's first platform of instant patch pumps for insulin (Figure 2c).

Imperium requires far fewer steps to commence therapy than any other known durable pump or insulin patch pump. A key reason for this competitive advantage is that it can be prefilled and pre-assembled with insulin. Just like with insulin pens, insulin providers can supply their brand of therapy in one fully integrated system ready for immediate patient use and covered under just one prescription. Unlike with all other known insulin pumps, there is no need for patients to load the device with insulin before use. Furthermore, patients do not

Figure 2: Unilife's platform of wearable injection devices: (a) The Precision-Therapy™; (b) The Flex-Therapy™; (c) The Imperium™.

require any extra pieces of equipment to be assembled with the pump before they can commence insulin therapy.

In addition to sharing the prefilled, pre-assembled simplicity of disposable pens, Imperium also has the therapeutic advantage of being an insulin pump. It comes supplied with a preset basal rate for continuous insulin infusion. On-demand bolus delivery is available to the user via a simple push of the button. Unlike with other insulin pumps, no complicated menu is required for bolus delivery.

Imperium is also capable of being a smart device, with the integration of Bluetooth LE connectivity paving the way for advanced informatics. Patients will be able to pair Imperium with an app on their smartphone. Authorised healthcare providers may also have access to data to help tailor the therapy to achieve glyacemic control. The compact size of Imperium, as well as other features including water-resistance, makes it ideal for convenient, extended multi-day wear.

ADDING VALUE IN VACCINES

Today, vaccines are either provided in vials or standard prefilled syringes. Both of these packaging formats require the use of multiple pieces of equipment, and require multiple steps to prepare and inject the dose. The complexity of dose preparation is especially evident with lyophilised drugs that require around a dozen steps alone for reconstitution.

To comply with needlestick prevention laws in the US and Europe, most vaccine providers supply their prefilled products in a standard prefilled syringe with a luer fitting. While such products can minimise bulk during transportation and storage, they also place the burden of compliance for needlestick prevention onto the individual healthcare facility.

Needlestick safety products, such as needle guards, that are commonly used with vaccines must be purchased and attached separately onto the prefilled syringe by a healthcare worker prior to use. Their bulky size may interfere with the injection process, and increase the time required for preparation.

Upon the delivery of a dose, the operator must first remove the non-sterile needle from the body and then manually activate the safety mechanism to render it safe. Often, the used syringe is disposed with the safety mechanism un-activated, creating a risk of injury to those downstream. These factors can significantly increase the time and cost associated with vaccine delivery.

Figure 3: The Unifill Finesse 1 mL Standard syringe features an automatic and fully integrated retraction system.

To overcome these and other challenges relating to the containment, shipment and delivery of vaccines, Unilife has created a complete, fully customisable portfolio of single and dual-chamber prefilled syringes. Most product configurations, including the Unifill Finesse 1 mL Standard syringe (see Figure 3), feature an automatic and fully integrated retraction system enabling operators to control the speed at which the needle is withdrawn directly from the body into the barrel to virtually eliminate infection risks associated with needlestick injuries or aerosolisation (blood splatter).

Dual-chamber systems with ventless, one-step reconstitution are also available with either staked, retracting needles or standard luer fittings. Amongst an array of customisation options, Unilife has created a proprietary telescoping plunger rod that significantly reduces product size to minimise shipping and storage costs.

With Unifill syringes being strongly user-preferred and accepted, pharmaceutical companies are able to leverage these feature and functionality advantages to further showcase the value of their vaccine brands against the competition.

ADDING VALUE IN AUTO-IMMUNE DISEASES

Many therapies targeting auto-immune diseases use disposable auto injectors. Whilst having some advantages over prefilled syringes including automatic dose delivery and the hiding of the needle, disposable auto injectors are commonly associated with number of challenges for both the patient and the pharmaceutical provider.

For pharmaceutical companies, there are additional costs to purchase and ship these bulky, single-use systems. Compared with a standard prefilled syringe, the cost per injection to utilise a disposable auto injector can increase by five to ten times or more. With most disposable auto injectors also having similar features and functionality, opportunities to utilise the device for brand differentiation are also minimised.

Auto injectors are primarily designed to inject doses of up to 1.2 mL in volume during a timeframe no longer than 15 to 20 seconds. Drugs which are unable to be formulated to suit delivery via a standard hand-held auto injector will typically require either injections to be given more frequently, potentially reducing brand preference rates, or require the transition to other device formats such as wearable injectors.

Figure 4: LISA is the world's first platform of smart, reusable and fully customisable auto injectors.

For self-injecting patients, disposable auto injectors have been linked with a range of user difficulties including limited portability, the extensive wait required for a biologic to warm to room temperature to minimise discomfort, pain associated with the speed of injection, and a lack of audible, tactile and visual indicators to confirm dose delivery.

To overcome these customer and patient unmet needs, Unilife has created LISA the world's first platform of smart, reusable and fully customisable auto injectors (Figure 4). Able to be used hundreds of times before replacement to minimise the cost per dose over a multi-year period, Unilife smart reusable auto injectors enable users to select the speed of injection to minimise potential pain or discomfort. Designed for use with Unifill prefilled syringes, the devices also enable safe, needle-free disposal. Capable of being integrated with Bluetooth LE connectivity for data informatics, the devices enable real time and historic access to data to support patient monitoring and compliance. A range of customisation features are available including a touchscreen display, pre-injection drug warming and RFID / NFC tag readers to check factors including drug expiration.

SUMMARY

The selection of a device platform by a pharmaceutical company should not only be based on how simple it is to customise, commercialise and use. As a preferred innovative device will ultimately play a significant role in the approval and commercial success of a target therapy, pharmaceutical companies should carefully consider how a device manufacturer can serve their long-term requirements with speed, agility and reliability.

In addition to having world-class, US-based manufacturing facilities and unparalleled innovation credentials, Unilife employs a dedicated team approach to customer programs. This approach enables Unilife to be fully responsive to a customer's needs in real-time, and encourages a close and collaborative relationship between the respective project teams. Unilife has also developed a company structure and culture that is highly customer-centric. Each project team that is established for a customer is composed of engineers, scientists and other experts from the drug delivery industry.

Unlike other companies where the business is predominantly based around materials or commodity components, Unilife was created from the ground up as a developer, manufacturer and supplier of sophisticated injectable drug delivery systems. It has a deep understanding of primary container technologies, and how they must be integrated into the effective production and functionality of a drug delivery system. From a customer perspective, this translates into having in Unilife a partner that has the expertise, processes and capabilities to take full responsibility for all aspects of the device and its integration within the overall drug-device combination product.

With Unilife also having a broad portfolio of injectable drug delivery systems, the company offers the neutrality to help pharmaceutical customers determine whether a particular molecule is best suited for use with a wearable injector, prefilled syringe, auto injector or a combination of two or more platforms. Unilife is ready to serve pharmaceutical customers under long-term partnerships to enable and enhance the delivery and commercial success of their injectable therapies.


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